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PREFACE

The publication in book form of the course in Gastroenterology given during the week of December 6–11, 1948, under the aegis of the American College of Physicians, is the outgrowth of an effort to make available to student physicians matriculated in the course a written record of the proceedings In view of the time and effort involved in recording transcribing and editing the proceedings it was decided to make available to other physicians the transaction of these meetings

Obviously, in arranging such short courses, no effort is made to cover, even in outline form, the broad field of Gastroenterology This course was arranged to appeal particularly to trained internists who wish to hear discussed some of the more recent advances, as well as certain controversial aspects of Gastroenterology

It was possible, during the brief period of one week, to discuss a number of the recent advances and unsettled problems of this branch of internal medicine For the most part, presentations were in the nature of symposia This permitted a coverage of basic experimental, physiologic, biochemical and pathologic aspects of the topic under discussion A panel discussion or question and answer period followed the more formal presentations of each brief symposium In addition, three periods of case presentations and clinical conferences were included Colleagues in radiology, surgery and the basic sciences pa ticipated in these discussions

Briefly, the principal topics comprised

(1) Certain aspects of the diagnosis and treatment of esophageal disorders

(2) Recent advances in our knowledge of gastric secretion including a discussion of physiologic and pharmacologic applications as well as a review of the present status of gastric analysis procedures

(3) Some recent advances in diagnosis and therapy of gastric neoplasms

(4) A review of some of the more recent contributions to our knowledge of peptic ulcer

(5) An outline of the application of neuropsychiatry to gastrointestinal problems

(6) A symposium on certain secondary gastrointestinal disorders, includ ing brief discourses on gastrointestinal allergy and abdominal symptoms of endocrinal origin

(7) Symposium on the pancreas, comprising a review of our knowledge of the physiology of the pancreas and emphasizing the importance of certain diagnostic procedures

(8) Symposium on the mechanism and significance of abdominal pain

(9) Symposium on the liver, stressing recent advances in diagnosis and treatment

(10) A review of certain experiences with non specific enteritis and entero-colitis

(11) A discussion of intestinal obstruction, comprising physiologic, biochemical, clinical and practical aspects

(12) Symposium on jaundice including a discussion of the differential diagnosis, of the postcholecystectomy syndrome and of dyssynergia

(13) Symposium on colonic diseases, including ulcerative colitis and neoplasms

The teachers participating in the course were drawn principally from the faculties of the Graduate School and the School of Medicine of the University of Pennsylvania However, a number of colleagues from elsewhere who have been responsible for important contributions in the field of Gastroenterology, kindly consented to participate These colleagues were drawn from the Jefferson Medical College and the Temple University Medical School in Philadelphia, and from certain medical institutions in New York City

The editor wishes to sincerely thank the faculty of the course for their splendid cooperation which in this instance entailed the prompt editing of their recorded talks and the arrangement of pertinent illustrations The recording and publishing of the course has been made possible through the kindness of W B Saunders Company The members of their staff have been most cooperative in making the task easier for the contributors and the editor

HENRY L BOCKUS, *Editor*

January, 1950

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The Esophagus

PYROSIS
Mechanism and Clinical Significance

HENRY TUMEN, M D

DR. BOCKUS *Our first topic this morning will be pyrosis This subject was selected because it constitutes one of the most frequent symptoms encountered by the gastro-intestinal internist*

DR TUMEN All physicians are called upon to treat a great many symptoms that are difficult to manage because the mechanisms responsible for them are so poorly understood We gastroenterologists, I think, have more than our share of these We not only have to worry about a great many varieties of abdominal pain, but we have to consider such symptoms as belching, bad taste in the mouth, coated tongue, flatulence and, not least of all, heartburn All of these may be symptoms of rather vague origin Often they present troublesome problems to both patient and physician

Heartburn is as Dr Bockus has mentioned, one of the most important of these symptoms—certainly one that has troubled many of us very often One of the curious things about heartburn is the fact that it is so difficult to define with any accuracy What we usually mean by heartburn is a rather indefinite burning or hot sensation, commonly located under the lower sternum or in the upper epigastrium with a tendency to radiate upward and to be associated with some type of acid regurgitation

MECHANISM

Surprisingly little work has been done in an effort to explain the mechanism of heartburn, but the work that has been done is extremely good and worthy of a great deal of consideration The studies which require comment are particularly those of Dr Chester Jones who was able to reproduce the symptom which patients call heartburn by distending the lower esophagus, particularly the area just above the cardia, by placing balloons there and inflating them He was also able to reproduce heartburn by distending the lower esophagus with fluids of various types This also has been done by others

The most important thing that has been brought out by this type of study is the fact that it is apparently not the nature of the fluid that is injected but the speed of the injection and the rapid distention of the lower esophagus, that is responsible for the reproduction of heartburn, that heartburn could be reproduced by the injection of water or of bicarbonate of soda solutions as well as by the injection of various acid media Jones has therefore, introduced the

cated, by the difficulty with which patients described specifically what they meant by heartburn Most of them simply placed their hands over their lower sternum and said This is the area that bothers me, this is where I have a sensation of burning " and ' When it gets bad, there is a tendency for it to radiate upward along the course of the esophagus, sometimes right into the pharynx or to the angles of the jaw, and sometimes it is associated with acid regurgitation

A lot of these patients had associated gastrointestinal symptoms Many of them had belching nausea, and epigastric pressure Some of them vomited and, of course, a great many of them had symptoms of the organic gastrointestinal diseases of various types that were the cause for consulting us

HEARTBURN IN RELATION TO ORGANIC DISEASE

We were very interested to determine whether or not we could demonstrate any relation between heartburn as a symptom and the presence of organic gastrointestinal disease in these patients In this particular group the only actual disease condition or, rather organic change that seemed to be consistently related to heartburn was the presence of hiatal hernia In this group there were 11 patients who had hiatal hernia Eight of them had heartburn as a very severe symptom, and in these 8 patients there seemed to be a definite correlation between the other symptoms that were associated with hiatal hernia, e g , the pressure, discomfort etc and heartburn There appeared to be the definite postural relationship to the development of heartburn which is characteristic of the other symptoms of hiatal hernia We felt that in this particular group of patients it was possible that this organic change at the cardiac end of the stomach and in the lower esophagus might be responsible for the production of the symptom Otherwise we were not able to trace any relationship between the presence of any organic disease of the gastrointestinal tract and the presence of heartburn in these patients Specifically we were not able to find that there was any relation between the presence of a peptic ulcer and the development of heartburn As a matter of fact, in this particular group of patients, ulcer was approximately twice as common in the patients who didn t have heartburn as in those who did and in those patients who had an ulcer and who had heartburn we were not able to get any history that would indicate any definite relation between activity of ulcer symptoms and the presence of heartburn We also found it was much easier to relieve the ulcer activity, i e , the pain due specifically to ulcer, in these patients than it was to relieve heartburn In other words, so far as we could determine, heartburn was not a symptom of ulcer activity *

* EDITOR S FOOTNOTE Obviously this would not be true in a large series of ulcer patients Pyrosis possessing the typical rhythm of ulcer distress does constitute the chief complaint of certain patients during ulcer activity and may be present only during the stage of ulcer activity In these instances the sensation of burning may be due to an entirely different mechanism It is unlikely that the stimulus arises in the lower esophagus Perhaps it may depend upon changes in pyloroduodenal tonus—the stimulus being inadequate to produce pain—or the pain sensibility of the patient may be less than average

theory that heartburn is associated with distention of the lower esophagus and some alteration of its neuromuscular activity, with the production very often of reversed peristaltic waves that travel up the esophagus at the time that the sensation is noted As a matter of fact, in the few studies that have been carried out under fluoroscopic control, this has been demonstrated

At the present time there is no definite agreement as to whether or not local mucosal changes in the lower esophagus are responsible for heartburn The idea has been suggested that there is some low grade esophagitis or that there are peptic glands of the lower esophagus that secrete acid, but there has never been any definite proof of this and most investigators are rather inclined to discount the idea that local mucosal changes in the esophagus produce the symptom

There is also very little unanimity of thought about the relation of heartburn to the character of the gastric contents that might be regurgitated into the esophagus at the time that heartburn occurs, although the idea has prevailed that hyperacidity may increase the ability of the gastric content to produce irritation of the lower esophagus, thus causing heartburn This has never been proved If we consider a specific kind of heartburn, the heartburn that is so frequently seen in pregnancy, apparently we have some definite evidence that the degree of acidity is not responsible for heartburn One of the characteristic changes in the physiology of the stomach during pregnancy is the lowering of the gastric acid level What is seen when these patients are studied is that they have an elevation of the stomach and a loss of gastric tone with a tendency to dilatation at the cardia and, sometimes, actual hiatal hernia formation There is ample opportunity for regurgitation of gastric contents into the lower esophagus Heartburn is often very severe in pregnant women even though their acid level has dropped off considerably during the period of observation This observation also tends to agree with the general idea that some disturbance in the neuromuscular mechanism at the lower end of the esophagus and changes in tone of the lower end of the esophagus are responsible for the symptom heartburn

Despite these various studies the thought certainly prevails among the laity, and to a very definite extent among physicians, that heartburn is a symptom of organic gastrointestinal significance and is particularly associated with hyperacidity, and that in many instances it is a symptom of ulcer—ideas which we believe are in need of being dispelled

INCIDENCE

In order to get some idea about the clinical significance of heartburn and some idea about its mechanisms, Dr Edwin Cohn and I made a survey during the last year of 120 consecutive patients to learn something about the incidence of heartburn and the various factors that were associated with it We found that of these 120 patients, who were not selected in any way, 46 had heartburn (approximately 38 per cent of the total) and that in 26 of these patients the symptom was really one of major importance to the patient and one that was a cause for a great deal of complaint We were struck, as I have already indi-

PERSONALITY PROBLEMS

In addition, we were interested to see that among these 46 patients, there were 8 patients—all of them men—who had very definite personality patterns which seemed in some way to be responsible for the development of this particular symptom They were extremely tense, resentful, argumentative individuals, of the type who are easily offended, very rigid in their attitude toward others, with a great deal of difficulty in understanding someone else s point of view As some of them said they got burnt up easily and found a lot of trouble in swallowing certain situations Those are terms that are borrowed from the psychosomaticists but they seem definitely to apply to these patients Many of them could describe specific instances and specific psychological problems which they recognized as being likely to cause tension and to produce heartburn the type of situation in which a man would find himself faced with disobedience on the part of an employee and, without doing anything to correct this, would simply let it go on to create a situation of tension in which he could regard himself as a martyr and abused Every time such a situation occurred, or was discussed, the patient would be conscious of a recurrence of heartburn In talking to these patients, it was often possible to reconstruct situations in which this definitely happened

It is true that this is not an unusual personality pattern and that it occurs in many individuals who don t have heartburn and yet in our own group, although a lot of the patients who didn t have heartburn were what could be called neurotic in the sense of being worrisome and apprehensive, they weren t the tense argumentative, hurried type of person such as I ve just described

TREATMENT

It seemed to us that these various factors required definite consideration in planning the treatment of heartburn Treatment by drug therapy is notoriously unsuccessful All types of agents have been tried—from bicarbonate of soda to hydrochloric acid and from belladonna to prostigmine Although many of these substances give temporary relief, very few of them are of any benefit from a permanent standpoint

It also seemed to us that simply altering the diet, except for eliminating certain foods known to disagree was not particularly successful So we began to spend some time with these patients to see what could be done from the standpoint of changing their eating habits They were given definite instructions about slowness of eating about the necessity for not overloading their stomachs, about avoiding lots of fluids at meal time, about stopping belching, and discontinuing gum chewing and carbonated drinks—correcting the various things which we felt had led to overloading of the stomach We were pleased to see in how many patients these simple instructions would result in the disappearance of heartburn As a matter of fact, of the 46 patients who had heartburn as a symptom, 34 received striking benefit from a little time spent in these general instructions, in discussion of the mechanism of the symptom and an explanation of its functional character and in correction of

We were likewise unable to determine that there was any relation between the presence of heartburn and diseases such as cholecystitis and cholelithiasis or the presence of the so-called irritable colon syndrome Patients with irritable colon very frequently had heartburn, but again we were not able to trace any specific and consistent relationship between the symptoms that were associated with the presence of irritable colon and the heartburn symptom We were also unable to demonstrate that the gastric acid level of these patients had anything to do with their heartburn There were acid levels of all types in patients with and without heartburn We agree, therefore, with observations of others that heartburn is not dependent upon any specific degree of acidity of the stomach We saw it with some frequency in patients who had low acid or no acid at all

We made some investigation as to food sensitivity in these patients We found that a great many patients with heartburn were people who had poor tolerance for certain foods like fried or greasy foods and onions, spices, etc Of course those are foods that disagree with a great many people We were surprised to see, however, that among those patients who had heartburn, these food intolerances were somewhat higher—definitely higher I should say—in frequency than in patients who didn t have heartburn We were not able, however, in any instance to make any definite statement that heartburn was related to food allergy, in so far as we could define this among these patients

Since heartburn did not seem to be a symptom of organic gastrointestinal disease and since it was not related in any way to the gastric acid level, and since it seems to have been shown to be dependent upon changes in the neuromuscular activity of the lower esophagus, we were interested to determine what it was about these patients that might possibly create these particular changes

HEARTBURN AND EATING HABITS

We made a study of the eating habits of these 46 patients with heartburn and found that a great many of them had very bad eating habits They were fast eaters, they were people who ate their meals under a great deal of tension, they were the type of people who sit down to lunch and discuss business and eat as fast as they possibly can in order to get the meal over with and get back to work They were the kind of people who eat in a family environment in which there is a lot of arguing at meal time, when everybody gulps his food so he can get the next word in That seemed to be a prevalent pattern of eating in many of these patients In addition these were people who usually ate large amounts In other words, they tended to overload their stomachs They drank a great deal of liquids with their meals, they had a tendency to drink a good many carbonated beverages They were many of them, gum chewers and most of them were patients who were air swallowers with good ability at aerophagy, and a lot of them were good belchers Most of these patients, briefly, were doing various things which we could conceive of as overdistending the stomach and possibly leading to a reversal of gastric peristalsis and regurgitation of gastric contents into the lower esophagus

is prolonged in this position), and a more detailed study of the area is done, multiple exposures are made for later study

It is necessary to use opaque materials of different consistencies so that the esophagus can be studied adequately The usual conventional mixture of barium and water is satisfactory for visualization of gross encroachment or displacement of the esophagus, transit time, and peristaltic activity However small lesions early carcinoma, superficial ulceration strictures etc , cannot always be appreciated because these can easily be obscured by the density and bulk of the conventional mixture A mixture of barium and acacia which leaves a fine film of barium adherent to the mucosa (after the bolus has been propelled onward) permits adequate mucosal study of the esophagus Finally a mixture of barium and water of the consistency of paste should be used in all cases It is not uncommon that this is the only mixture in which an early intra luminal lesion manifests itself Not only must the patient be studied using various barium mixtures, but the patient must be rotated through 360 degrees in order that the walls and marginal contours are visualized throughout the entire extent of the esophagus Otherwise early esophageal lesions can easily be overlooked

Both the clinician and the radiologist realize that the esophagus may be displaced from its normal position by adjacent structures, normal and pathologic such as enlarged thyroid, prominent aortic knob, prominent left auricle and mediastinal tumors What is not usually appreciated is that these sites where the esophagus is commonly affected by extrinsic pressure are also the sites of intrinsic lesions It is therefore important that any abnormality be recorded on film by multiple exposures so that a careful evaluation of the abnormality can be done

Today the radiologist is no longer content merely to take advantage of the different consistencies of barium mixture and positional maneuvers, but uses various physiological factors which may aid him in more adequately demon strating esophageal abnormalities This is particularly true when he is dealing with a small sliding hiatal hernia which may not be appreciated in the erect and even in the recumbent positions but with the use of the Valsalva maneuver or any other means of increasing intra abdominal pressure, the hernia is exaggerated and clearly visualized It is not uncommon for a roentgenologist who routinely takes multiple exposures of the lower end of the esophagus subsequent to the Valsalva maneuver to demonstrate hernias which account for the patient s symptoms

Furthermore, in view of the recent advances of thoracic and esophageal surgery it is no longer sufficient for the roentgenologist to diagnose a lesion, he must demonstrate the full extent of the abnormal process, its location mucosal abnormalities and the state of the esophagus adjacent to the lesion This of course becomes obvious if one stops to consider the various surgical approaches that become necessary when considering lesions in various loca tions within the esophagus

In the more obvious lesions of the esophagus the function of the roentgenologist is to obtain as much information as possible in an attempt to aid

faulty eating habits Those patients, of course, who had deep-seated personality problems presented very difficult situations We had 3 who were referred to psychiatrists and who, under psychiatric care, were able to get rid of a good bit of their tension and make some definite personality readjustments We believed that this therapy was associated with relief of heartburn

As a result of this relatively small and rather subjective study, we came to the conclusion that of the various symptoms with which we had to deal, heartburn was certainly one in which there was a very pronounced "functional element That functional element was very often a mechanical one and related to habits of eating which usually could be easily corrected, in other instances, not very many, heartburn seemed to be a manifestation of a neurosis—what Dr Bockus likes to call a 'monosymptomatic neurosis' —which seemed to have a psychogenic origin and which could be relieved by psychotherapy if properly applied

WHAT THE GASTROENTEROLOGIST EXPECTS FROM THE ROENTGENOLOGIST IN DIAGNOSIS OF ESOPHAGEAL LESIONS

DAVID E ZION, M D

The examination of the esophagus is one of the more difficult studies which the roentgenologist performs This is in part due to the fact that the esophagus is located within the thoracic cage making palpation impossible The transit time of the bolus through the esophagus is rapid and all observations must be made in a comparatively short time And finally, because of its location within the thoracic cage and its position anterior to the spine and posterior to the cardiac silhouette, adequate visualization of the lower half of the esophagus is at times difficult It is therefore not surprising for even an extremely careful fluoroscopist to overlook small lesions during fluoroscopy, the examination of the esophagus is considered inadequate without multiple exposures of the mucosal pattern and of the distended esophagus with the opaque material The roentgen examination is done in both the recumbent and erect positions and in at least three projections Films are exposed in the anteroposterior, lateral and oblique projections Since the lower end of the esophagus is the seat of numerous pathologic processes, a seriographic study of this portion of the esophagus is done even though fluoroscopically this may appear to be normal

We find that the fluoroscopic study of the esophagus in the erect position is an excellent method for obtaining indications of slight degrees of dilatation slight delays in transit time and slight displacement Once these areas are located, the patient is placed in the recumbent position (since the transit time

it is only after repeated studies that a definite diagnosis can be made Sometimes the roentgenologist cannot make a conclusive diagnosis and it is necessary for the clinician to call upon the endoscopist for assistance or even the surgeon in order to obtain a definitive diagnosis It is not uncommon that retained materials in the esophagus produce numerous filling defects which may simulate neoplasms, and their true nature is not confirmed until endoscopy or repeated aspiration studies are done

ILLUSTRATIVE CASES

Case 1 The diagnosis of achalasia is as noted before extremely difficult, because it is not uncommon for dilatation at the lower end of the esophagus

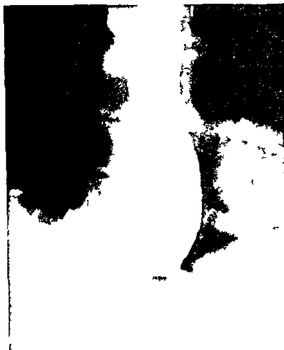


Fig 1 Carcinoma of the lower portion of the esophagus simulating achalasia

to be due to causes other than the so called cardiospasm It is important that an adequate mucosal pattern be obtained of the narrow area so that an attempt at a differential diagnosis can be made In this particular case the irregularity of the mucosal pattern at the strictured area suggested the possibility of neoplasm which was confirmed by endoscopy (Fig 1)

Case 2 Small hiatal hernias of the sliding type, which are extremely common in the older individual, are easily demonstrated by having the patient increase intra abdominal pressure so that the hernias become manifest (Fig 2) It is important to note whether there is regurgitation from the hernia into the esophagus or whether there is merely a small hiatal hernia

the clinician in his decision concerning proper therapy It is not uncommon for the roentgenologist to assist the gastroenterologist by informing him as to the size, the degree of reduction if any in the erect position, and the optimum position for emptying of the hernia The percent of regurgitation of the opaque material from the stomach into the hernia, from the hernia into the esophagus, if any, can be learned during the fluoroscopic observation and recorded on film It is extremely important that an adequate mucosal pattern of a hernia be obtained during the roentgen study in order to determine whether or not associated pathology in the hernia exists Multiple exposures are made not only for the purpose of recording the state of the mucosa of the hernia for future reference, but also, as we have learned from experience, because fluoroscopic observations in themselves are not sufficiently reliable if a critical analysis is to be obtained In almost all cases of moderate or large-sized hernias, distortion of the mucosal pattern is present, and, if sufficient film studies are not made, then small ulcerations, gastritis or even neoplasms can easily be overlooked At times, even upon extensive review of multiple adequate exposures of the hernia, the roentgenologist is uncertain whether he is dealing with an extensive gastritis, or an early neoplasm within a hernia In these cases even though the roentgen study is not definitive it is sufficient to alert the clinician of the various possibilities that exist and, since he has other laboratory procedures at his command, to assist him in his diagnosis This pertinent information may be the first clue which may lead to the final diagnosis It is therefore obvious that although the roentgenologist may account for numerous symptoms of the patient with a diagnosis of hiatal hernia, the diagnosis in itself is incomplete unless the roentgenologist can definitely state that no associated pathology exists

It is not uncommon for the roentgenologist to ask the clinician to have the patient return for a second study of the esophagus even after having taken multiple exposures of it and having had the patient in his office for what is considered by some clinicians an abnormal length of time This is particularly true of cases with minimal areas of constriction of the esophagus which fluoroscopically appear to be transient, yet on multiple exposures appear to be constant The conscientious roentgenologist accordingly must have the patient return so that the particular area in question can be studied and re evaluated in light of the previous findings which may or may not confirm the former impression Two and sometimes three independent studies of the esophagus must be done at times in order to demonstrate varicosities It is our opinion that complete and definite studies cannot always be accomplished on the initial study and we feel that we are not imposing upon the clinician is asking the patient to return for subsequent examination, for if the study was indicated in the first place then a definitive study is necessary

The diagnosis of achalasia is at times an extremely difficult one for the roentgenologist to make It is not uncommon for dilatation at the lower end of the esophagus to be due to lesions other than so-called cardiospasm Scarring from previous inflammatory disease, achalasia, scarring from a chemical burn, and neoplasms at times closely simulate one another and at times

produced The clinical symptoms may differ and this information can be obtained by the roentgenologist with a little care

At least three or four different maneuvers are done for every patient when the lower esophagus is studied. (1) Observations of the liquid bolus as it passes down and through the hiatus (2) Study of the mucosal pattern by means of a thick mixture (3) Making various changes in pressure in the intra-abdominal cavity in order to attempt to demonstrate hernias (4) Studying the esophagus in both the recumbent and the erect position Here a Valsalva maneuver demonstrating a hernia is much more effective than the other maneuvers

Fig 4

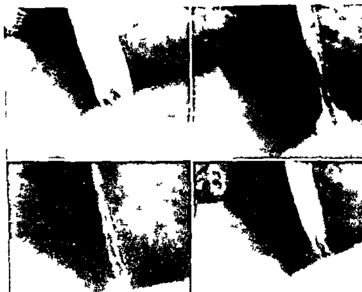


Fig 5

Figs 4 and 5 Varices of the lower end of the esophagus partially obscured when esophagus is overdistended with barium

Case 3 Large hernias that occur not only must be demonstrated but the mucosal pattern within the hernia must be visualized in order to rule out associated lesions which occur in some hernias Presence of the hernia does not exclude carcinoma within the hernia or gastritis (Fig 3)

Sometimes it is impossible to perform endoscopy for clinical reasons and the only procedures that may be available to the clinician are roentgenology and serio-roentgenograms of the mucosal pattern of the hernial sac Frequently the roentgenologist cannot differentiate between a hypertrophic gastritis and carcinoma but after a proper medical regimen, repeated examinations may show changes which may lead to a definitive diagnosis

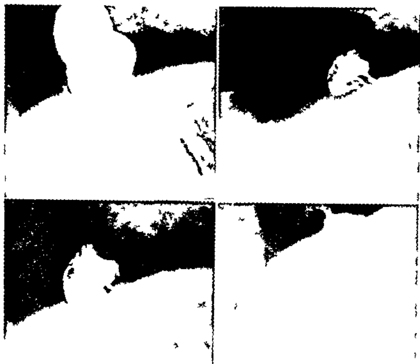


Fig 2 Small hernia more clearly demonstrated following a Valsalva maneuver



Fig 3 Moderate mucosal distortion due to gastritis in a large hernial sac

well over a period of years with conservative management Roentgenograms that illustrate two of our cases that did not respond to dilatation are shown in Figs 6 and 7

The S- or sigmoid shaped esophagus does not respond as well to conservative management as do the more common flask- and spindle-shaped ones Very frequently the patients who come to surgery give a history that dates back many years Often there have been long periods during which only a very small amount of fluid passed into the stomach



Fig 6 Preoperative roentgenogram in a case that did not re pond to dilatation

When operation is contempated, an adequate preoperative regimen must be instituted The broncho esophagologist may be able to pass a Levin tube for feeding purposes under guidance through the esophagoscope Usually a tube will not pass into the stomach if it is merely swallowed

We have approached these lesions surgically through a left upper rectus incision or by a combined abdomino thoracic approach In the latter, the abdominal incision extends across the left costal margin into the chest I believe that the abdominal approach is adequate, and there is less postoperative incisional pain Figure 8 (*1* and *3*) graphically represents the procedures

Case 4 This may mean that multiple exposures, taken on the same day, do not demonstrate varices, while multiple exposures on subsequent days may demonstrate them Extensive varicosities partially obscured by the bolus coming down, and demonstrated when the bolus passes due to the coating of the mucosal pattern by the residual barium, are shown in Figs 4 and 5

NEWER DEVELOPMENTS IN THE SURGERY OF THE THORACIC ESOPHAGUS

HERBERT R HAWTHORNE, M D

DR BOCKUS *Great advances have been made by the thoracic surgeons and advantages are being taken of these advances in the utilization of surgical procedures on the esophagus As a result of improved surgical technic and advances in our knowledge of anesthesia, the esophagus may now be dealt with surgically throughout its entire length*

DR HAWTHORNE

ESOPHAGEAL DIVERTICULUM

The esophageal or, more correctly, the pharyngeal diverticulum has been successfully treated by operation for many years Most surgeons now agree that a one stage operation with excision of the sac and inversion of the neck is the procedure of choice A diverticulum in this region should be operated upon as soon as a definite sac is formed

I believe that it is important to have the sac thoroughly emptied and cleansed by a broncho esophagologist prior to operation Occasionally a patient in a poor nutritional state resulting from longstanding inability to take adequate nourishment will be immeasurably improved by preoperative feeding Under these circumstances, a Levin tube passed under guidance through the esophagoscope will usually be tolerated by the patient for a few days and a sufficient amount of nutrition can be given by this route If the tube is not tolerated, intravenous feedings and blood transfusions will be required

I have briefly mentioned the pharyngeal diverticulum in order to compare the management of this lesion to a diverticulum of the lower end of the esophagus The latter rarely requires surgical intervention since most of these lesions are asymptomatic and are discovered only in the course of routine study

FUNCTIONAL MEGAESOPHAGUS

The functional megaesophagus or idiopathic dilatation of the esophagus should be treated initially by dilatation Most of these patients will do fairly



Fig 9 Preoperative roentgenogram of cardio-esophageal junction in a case which did not respond to dilatation over a period of years Note extreme stenosis and dilatation of esophagus above



Fig 10 Postoperative roentgenogram of case in Fig 9 Note large stoma and free flow of barium



Fig 7 Preoperative roentgenogram in a case with sigmoid shaped esophagus

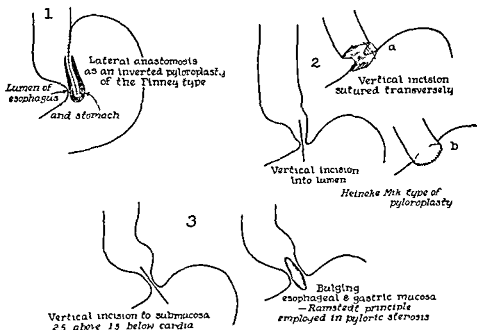


Fig 8 Graphic representation of the three surgical procedures usually employed for idiopathic dilatation of the esophagus

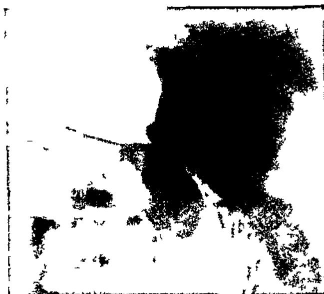


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Fig 10 Postoperative roentgenogram of case in Fig 9 Note large stoma and free flow of barium

that I have employed Vertical incision into the lumen with transverse suture of the opening, Fig 8 (*2*), is another method of enlarging the cardio-esophageal junction The Heller procedure, Fig 8 (*3*), has been employed by Rodney Maingot and he reports excellent results with it This technic has been utilized in my last two cases and the results have been most satisfactory This is merely a Ramstedt type of operation in which the vertical incision is made *down to the mucosa and the muscular coats are spread apart until the mucosa* bulges Formerly, we performed an esophago-gastric anastomosis, Fig 8 (*1*), essentially an inverted Finney type of pyloroplasty

We have encountered only one case in which there was a thickened ring at the cardio-esophageal orifice In most instances, there is only a moderate hypertrophy of the muscle layer at the lower end of the esophagus

Postoperatively, there is often very little change in the size of the enormously dilated esophagus Figure 9 is a preoperative roentgenogram of a case that did not respond after three years of dilatation Figure 10 represents the postoperative result in this case The dilatation may remain for several years A full diet can be tolerated most of the time However, some of the patients will have short periods of spasm and will be forced to return to a liquid diet for a few days This is one of the features of cardiospasm that is difficult to understand, since the esophagogastric anastomosis is more than twice as wide as the normal diameter of the esophagus Most of the patients do obtain long periods of freedom from the obstruction and respond very well to the intake of food We hope that the Heller procedure that has recently been employed will result in complete freedom of spasm

ESOPHAGEAL ATRESIA AND TRACHEO ESOPHAGEAL FISTULA

Although esophageal atresia and tracheo-esophageal fistula are of more interest to the pediatrician, you may be interested in a brief summary as to how these newborn babies are treated Figure 11 demonstrates a technic developed by Ladd, which we have employed successfully End to-end anastomosis is preferable when approximation is feasible This operation has opened new fields in the development of esophageal surgery The final stages of the anterior skin tube procedure will probably be eliminated by waiting until the child is older, and some form of intrathoracic anastomosis can then be completed

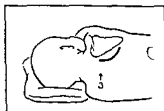
BENIGN STRICTURE OF THE ESOPHAGUS

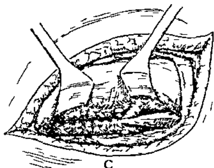
Benign strictures *of the esophagus may now be dealt with in a satisfactory* manner A transthoracic operation similar to the procedure for resection of a carcinoma is employed As a result of the development of surgery for malignant lesions, it has been found that the stomach may be brought up and anastomosed to the first portion of the esophagus This has eliminated the use of the undesirable anterior skin tube, and has much to offer to the many unfortunates who were *forced to go through life with a permanent* gastrostomy

CARCINOMA OF THE ESOPHAGUS

Carcinoma of the esophagus represents about 5 per cent of all carcinomas found in the body. The more common squamous epithelioma with its slow growing characteristics, has every chance to offer a higher five-year survival rate than carcinoma of the stomach.

It is not my purpose to dwell on the symptoms and diagnosis. In a doubtful case, it can now be said that an exploratory thoracotomy is almost as safe a





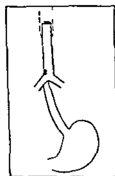


Fig 11 Inserts show (A) incision and (B) position of upper blind end of the esophagus and the lower end of the esophagus connected to the trachea. C shows the pleura reflected forward, branch of azygos vein divided and the tracheo-esophageal fistula exposed.

procedure as an exploratory laparotomy. A biopsy of the lesion should always be attempted through the esophagoscope before operation, or in case of failure to obtain a section of tissue, a Papanicolaou cell smear method is employed.

Lesions located at any place from the cardiac end to a short distance above the aortic arch may be approached through the thorax. In the very high lesion, a combined thoracic and cervical approach may be required.

The operability of the lesion cannot be determined until it is exposed. However, some cases will be rejected on obvious evidence of widespread metas

tases A boring interscapular pain usually indicates extensive spread The occasional tracheo-esophageal fistulization by the tumor will, of course, contraindicate surgery We believe that if the tumor can be freed, and even if there is evidence of early involvement of the liver, a palliative resection to relieve the obstruction is a worthwhile procedure Certainly it is far better than a gastrostomy This statement also holds true if there is spread to the hilar glands or the aortic chain of nodes These more advanced cases do not usually recur at the site of resection before the patient dies of metastatic spread of the disease A lesion near the aortic arch which presents symptoms of involvement of one or both recurrent laryngeal nerves usually is found to be inoperable

OPERATIVE PROCEDURE

Briefly, the operative procedure consists of opening the pleural cavity and searching for evidence of spread Then a survey of the lesion is made The diaphragm is not opened until it has been determined whether the tumor can be separated Sometimes there is no evidence of metastasis, but the lesion has invaded the wall of the aorta This situation will preclude any attempt at surgery, and therefore we do not believe that there is any advantage in opening the abdomen first by a combined abdominothoracic approach An exception to this can be made for lesions of the cardiac end of the stomach

Metastases to the nodes around the left gastric artery will take place from a lesion as high as the aortic arch Above this level, the metastases spread along the inferior thyroid artery to the deep cervical nodes

In the lower lesions, it is particularly important to determine whether it is technically possible to remove an involved mass of glands that are fixed to the cardiac end of the stomach This can only be determined after the diaphragm has been opened

If the lesion is low, the lowermost end of the transected stomach is formed into a tube If the tumor is behind or above the aortic arch, the entire stomach may be brought up to a position above the aortic arch to the uppermost end of the thoracic esophagus Some of the lesions of the lower esophagus require removal of the spleen and a portion of the distal end of the pancreas

Occasionally a total gastrectomy is required because of extensive involvement along the lesser curvature The lower end of the stomach is not employed for the anastomosis In this instance the jejunum may be transected 8 to 12 inches distal to the ligament of Treitz, and the single tube is then brought up to the divided esophagus The mesentery of the proximal jejunum is divided so that the vascular supply in the arcade will be preserved in the manner proposed by Rienhoff The distal end of the jejunum is then anastomosed to the under surface of the most dependent portion of the loop which was anastomosed to the esophagus Some surgeons now prefer to routinely employ the jejunum rather than the lower end of the stomach for the anastomosis They believe that it is preferable to have the small bowel in the chest rather than to have the pleural space occupied by the relatively large stomach

PREOPERATIVE CARE

Preparation of the patient for operation will require a longer period of time when a malignant tumor is present than would be required for various benign lesions Unfortunately, most of the malignant cases show the effects of poor nutrition Do not forget that the slow growing squamous cell carcinomas may have caused enough obstruction to give one the impression that an advanced malignant growth is present If no evidence of spread of the disease can be found, then every effort at forced feeding should be made In the obstructed case, the broncho-esophagologist may be able to pass a Levin tube under direct vision The feeding tube has been tolerated for as long as two or three weeks in several of our cases If it is not possible to pass a tube, then a pre-



Fig 12 Small nonobstructing carcinoma of the esophagus without gross evidence of spread Survival time after resection only fifteen months

liminary jejunostomy is performed It is surprising to see how marked a gain in weight and strength follows a forced feeding regimen One of our patients gained 8 pounds in three weeks

In addition to other feedings protein hydrolysates mixed with milk or broth are given to provide an intake of 150 to 200 gm of protein daily Two patients who had been decompensated prior to operation were successfully operated upon following adequate preoperative preparation Preliminary jejunostomies were performed in both of the cases in order to avoid overloading the circulation with intravenous alimentation postoperatively Feeding through the jejunostomy is possible twenty four hours after operation

POSTOPERATIVE CARE

Blood transfusions are required before, during and after operation The postoperative care requires constant supervision These operations are not

only on the alimentary tract, but involve the pleural cavity as well Lung complications are common Atelectasis may be massive and require bronchoscopic drainage Pleural effusion and occasionally a mediastinitis may occur as the result of an extensive resection However, with the use of antibiotics, empyema can be prevented

Delay in emptying of the gastric tube below the anastomosis may occur in some cases due to transection of the vagus nerves Liquids and food regurgitate to an annoying degree in an occasional case, but this gradually decreases Many of the patients have a mild burning sensation in the epigastrium for some time following operation, but the gastroenterologists have been able to control this with diet and medication

RESULTS

Figure 12 illustrates an unusually small and nonobstructing lesion for which, however, survival time was only fifteen months The survival time in our series is about twelve to fifteen months Two patients are still well, clinically and by x ray, over two years after operation Table 1 shows our mortality rate up to January 1, 1948

Table 1 Operative Mortality Carcinoma of the Esophagus

Cases to 1/1/48	31	
Resected	26	
Overall mortality rate	22 8%	
Causes of death		
Pulmonary embolism		2
Coronary thrombosis		1
Tension pneumothorax		1
Tear in aorta sutured survived fourteen days		1
Diffuse mediastinitis		1
Diffuse carcinomatosis		1

This will decrease with added experience Resection that was attempted in several of the earlier cases that had extensive mediastinal involvement would not now be considered

The mortality is now very low for benign surgical lesions of the esophagus and the operative results are very satisfactory In the major clinics, the mortality following operations for carcinoma of the esophagus has been greatly reduced Although this surgery is relatively new, enough of these operations have been performed to allow in the very near future an assessment of its value in the terms of a five-year survival rate

Gastric Secretion

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EFFECT OF PARASYMPATHOMIMETIC DRUGS ON HUMAN GASTRIC SECRETION

ARTHUR M SCHOEN, M D

Parasympathomimetic drugs have been used during the past seventeen years in the symptomatic treatment of certain organic and functional disorders They have been employed because of their vasodepressor effect in such peripheral vascular diseases as hypertension, Buerger s disease and Raynaud s disease These same drugs may also stimulate contraction of smooth and skeletal muscle, and consequently have produced beneficial results in paralytic ileus and myasthenia gravis The dual effect of these drugs i e, relaxation of the smooth muscle of blood vessels and concurrent contraction of the gastrointestinal musculature may at times seem paradoxical However the pharmacologic responses to these agents may be explained satisfactorily in the light of newer concepts of their mode of action especially as related to the mechanism of nerve stimulation of tissue

THE CHEMICAL TRANSMISSION OF NERVE IMPULSES

According to the theory of the chemical transmission of nerve impulses finally established by the work of Otto Loewi in 1921 the stimulation of an efferent nerve to a muscle or gland produces a response through the liberation of a chemical substance from the nerve ending The chemical substance liberated is either acetylcholine or an adrenalin like substance which Cannon has named sympathin The type of nerve stimulated determines which of the two substances will be produced When a cholinergic nerve fiber is stimulated acetylcholine is liberated, when an adrenergic fiber is stimulated sympathin is formed at its terminal The essential feature of Loewi s theory is that all efferent nerve impulses are mediated to ganglion cells and effector cells* by one or the other of these two chemical substances The term parasympathomimetic introduced by H H Dale in 1914, was used to describe the pharmacologic effects of acetylcholine which drug he noted mimicked the response following stimulation of parasympathetic nerves He also noted that atropine suppressed the parasympathetic effects of acetylcholine and at the same time he observed a rise in blood pressure comparable with that following stimulation of peripheral sympathetic ganglia It was later shown by Loewi that acetylcholine was liberated not only by the pre and postganglionic fibers

* The term effector cells includes all gland cells all smooth muscle cells and the striated muscle cell of the heart Effector cells are innervated by both the sympathetic (postganglionic adrenergic) and parasympathetic (postganglionic cholinergic) nerves

the parasympathetic nervous system but also, to various degrees, the response to stimulation of the sympathetic system and somatic motor nerves

Figure 13 is a schematic representation of the distribution and connections of efferent nerve fibers of the autonomic and voluntary nervous systems It shows that acetylcholine is liberated at all autonomic ganglion cells of both the sympathetic and parasympathetic systems, at the adrenal medulla by pre ganglionic fibers of the sympathetic system at skeletal muscle by somatic motor nerves and at the effector cells innervated by postganglionic fibers of the parasympathetic nervous system As shown, sympathin is produced only at the effector cells innervated by the postganglionic fibers of the sympathetic system Since other choline compounds (choline-containing parasympathomimetic agents) are also capable of acting similar to and at the same sites as acetylcholine, it follows that parasympathomimetic drugs may mimic the response following stimulation of either, or both the sympathetic or para sympathetic nervous systems The effect produced by the action of a particular choline compound is determined, to some extent, by its specificity of action, i e , whether it produces its greatest response by stimulation of the sympathetic or parasympathetic ganglia, skeletal muscle or effector cells innervated by postganglionic fibers of the parasympathetic system For example, if it were desirable to stimulate only intestinal motility by use of a parasympathomimetic agent then that agent must act by causing a stimulation of the smooth muscles innervated by postganglionic fibers of the parasympathetic system only Furthermore, the stimulation should be limited to the intestinal musculature, and should not affect other structures innervated by postganglionic cholinergic nerves, such as heart muscle or glands The generalized response to acetylcholine would preclude the use of such a drug for producing a specific response Therefore other choline derivatives have been studied in an effort to determine if any possess specificity of action

CLASSIFICATION OF PARASYMPATHOMIMETIC DRUGS

Parasympathomimetic drugs may be classified in three groups as shown in the outline below Group 1 includes certain alkaloids which act selectively on

Group Classification of Parasympathomimetic Drugs

Group 1 DRUGS WHICH ACT DIRECTLY ON EFFECTOR CELLS INNERVATED BY PARASYMPATHETIC NERVES Pilocarpine muscarine arecoline
Group 2 ANTI CHOLINESTERASES Physostigmine prostigmine DFP
Group 3 CHOLINE ESTERS Acetylcholine mecholyl doryl urecholine

cells innervated by postganglionic cholinergic fibers This group is represented by pilocarpine arecoline and muscarine The pharmacologic response to these alkaloids truly mimics the response to stimulation of the entire para sympathetic nervous system Since all structures innervated by the parasympathetic system are markedly stimulated by these drugs they are of no value clinically because of the side effects which result from this non-specificity of action

The second group consists of anti cholinesterases It includes physostig

of the parasympathetic nervous system, but also at all ganglion cells of the sympathetic system, as well as at the neuromuscular junction of somatic motor nerves with skeletal muscle

It is now generally accepted that since acetylcholine stimulates both the sympathetic and parasympathetic ganglia, the organ response is governed by the net influence exerted by the two autonomic nervous systems If acetylcholine is injected into a non atropinized animal, the parasympathetic system exerts the greater influence and consequently vasodilatation occurs If, on the other hand, atropine had been administered prior to acetylcholine, the parasympathetic stimulus would be blocked at the blood vessel However, the

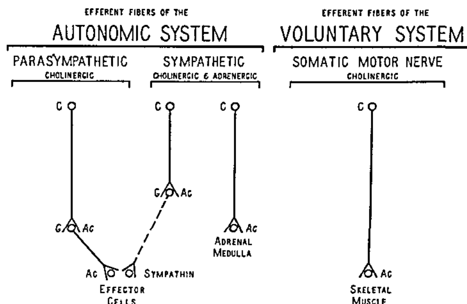


Fig 13 Schematic representation of the distribution and connections of efferent nerve fibers of the autonomic and voluntary nervous systems

C = Cells of central origin located in the brain or spinal cord G = Peripheral ganglia showing synapse of preganglionic nerve fiber with postganglionic cell body The effector cell may be smooth muscle heart or gland cell AC = Site of liberation of acetylcholine ——— = Cholinergic nerve fibers - - - - = Adrenergic nerve fiber

sympathetic stimulus, mediated by acetylcholine at the ganglion and by sympathin at the myoneural junction of the vessel, is unaffected by atropine Thus, in the atropinized animal, acetylcholine stimulates only the ganglion cells of the autonomic nervous system, thereby causing the postganglionic fibers of the sympathetic nerves to release sympathin which then produces vasoconstriction and a rise in blood pressure

The term parasympathomimetic,' in keeping with Dale s original definition, is used today to designate those autonomic drugs which act upon structures that are innervated by cholinergic nerves Contrary to Dale s original belief, it is now recognized that acetylcholine and certain other choline containing compounds mimic not only the response to stimulation by

GENERAL RESPONSE OF GASTRIC SECRETION AND EMPTYING TO PARASYMPATHOMIMETIC DRUGS

With the exception of the anti-cholinesterases, the response of gastric function to parasympathomimetic agents is not dependent on any influence from the central nervous system The response to these drugs depends solely upon the inherent functional ability of the glands and musculature Thus, drugs of Groups 1 and 3 may produce parasympathetic like effects on the stomach after the vagus nerve trunks have been severed Furthermore, certain of these drugs, e g , doryl and acetylcholine but none of Group 2 or urecholine, may mimic the sympathetic response even after section of the splanchnics They will not do so if the celiac ganglion or its efferent fibers to the stomach have been interrupted Following the administration of a parasympathomimetic agent, a normal stomach, or one associated with a peptic ulcer, responds with an increase in motor and secretory function If atrophy of the gastric mucosa is present, motor activity but not secretion, may be stimulated After bilateral vagotomy, parasympathomimetic drugs, with the exception of Group 2, may be expected to stimulate both secretion and motility Drugs of Group 2 may stimulate secretion slightly and diminish emptying markedly if the stomach has been freed of vagal influence

EXAMPLES OF GASTRIC RESPONSE TO PARASYMPATHOMIMETIC DRUGS AFTER VAGOTOMY

In order to show the effect of several different autonomic agents on gastric secretion and emptying data obtained from a single patient are shown in Table 2 The method used for obtaining these data is outlined briefly on page 31 The subject was a sixty four year old colored male with a history of duodenal ulcer disease for twenty years and who had experienced several bouts of complete gastric obstruction during the one year preceding surgical treatment of his ulcer and retention On August 29 1946 a transabdominal bilateral vagotomy and anterior gastroenterostomy were performed * All symptoms were relieved immediately following surgery and none have recurred Three satisfactory insulin tests have been performed after vagotomy and all have been negative The last one was performed twenty five months postoperatively

In demonstrating the effect of parasympathomimetic agents on gastric function, there are several reasons for presenting data from a person with vagotomy First, these agents have been and are being used to relieve gastric retention which has occurred in some persons following vagotomy Secondly, the effect of these drugs may be more pronounced after vagotomy because of the stimulation of gastric activity which they produce in a stomach which has been relatively quiet Finally, the 'paradoxical response to prostigmine after vagotomy as contrasted with the response to other parasympathomimetic agents, may be used to illustrate the different mechanism of action of these different types of drugs

* Surgery was performed by Dr R Arnold Griswold University of Louisville Louisville Kentucky

mine, prostigmine and di-isopropyl fluorophosphate (DFP) These drugs act by inactivating cholinesterase Acetylcholine, which is liberated by cholinergic fibers or which is injected into the body, is rapidly destroyed by an enzyme, cholinesterase This enzyme is normally present in the body and is especially abundant in those tissues innervated by cholinergic fibers Its action is to hydrolyze acetylcholine, thereby producing choline and acetic acid, neither of which exerts appreciable parasympathomimetic effect The protection afforded acetylcholine by the anti cholinesterases, prostigmine and physostigmine, results from their temporarily inactivating cholinesterase The alkyl ester of fluorophosphoric acid, DFP, irreversibly inhibits cholinesterase and consequently exerts a more profound effect than either of the other two drugs If cholinesterase is inactivated, acetylcholine may then exert its action in a more intensified manner and for a much longer period of time Therefore, the administration of anti cholinesterase drugs is followed by a response similar to the continuous and intensified action of acetylcholine For this reason they are classified as parasympathomimetic agents, even though they do not act directly on structures innervated by cholinergic nerves Since acetylcholine is capable of stimulating all peripheral ganglia and all effector cells innervated by cholinergic fibers, the anti-cholinesterase compounds produce a response similar to that following a widespread discharge of all cholinergic fibers Since such a response is altered by other variable factors existing at the time of the nervous stimulation, the net effect is unpredictable and consequently no specificity of action is manifested

The third group of parasympathomimetic drugs is represented by the choline esters Acetyl-β-methylcholine chloride (mecholyl) represents one of the first synthetic parasympathomimetic drugs to be of use clinically The value of this synthetic ester depends on its relative immunity to hydrolysis by cholinesterase and also to its more limited sites of action The latter characteristic may be demonstrated by the absence of a rise in blood pressure following administration of the drug to an atropinized animal Such a response is evidence that mecholyl does not stimulate all ganglion cells of the sympathetic nervous system (As mentioned previously, acetylcholine produces a rise in blood pressure in the atropinized animal) Compared with acetyl choline, the response to mecholyl is of longer duration and it more closely mimics the response to stimulation of only the parasympathetic nervous system

Carbaminoyl-choline chloride (doryl) and carbaminoyl-β methylcholine chloride (urecholine) are parasympathomimetic drugs which seem to be unaffected by cholinesterase Their action is neither augmented nor prolonged by prostigmine or physostigmine Therefore, their duration of action is longer than that of mecholyl Both of these drugs act more specifically on the gastrointestinal and urinary tracts than the previously mentioned agents Urecholine has less effect on ganglion cells than does doryl It also is less effective in its action on effector cells innervated by cholinergic fibers In other words, urecholine is a milder acting drug than doryl, and it is possibly somewhat more specific for the gastrointestinal tract

GENERAL RESPONSE OF GASTRIC SECRETION AND EMPTYING TO PARASYMPATHOMIMETIC DRUGS

With the exception of the anti-cholinesterases, the response of gastric function to parasympathomimetic agents is not dependent on any influence from the central nervous system. The response to these drugs depends solely upon the inherent functional ability of the glands and musculature. Thus, drugs of Groups 1 and 3 may produce parasympathetic like effects on the stomach after the vagus nerve trunks have been severed. Furthermore, certain of these drugs, e.g., doryl and acetylcholine but none of Group 2 or urecholine, may mimic the sympathetic response even after section of the splanchnics. They will not do so if the celiac ganglion or its efferent fibers to the stomach have been interrupted. Following the administration of a parasympathomimetic agent, a normal stomach, or one associated with a peptic ulcer, responds with an increase in motor and secretory function. If atrophy of the gastric mucosa is present, motor activity, but not secretion, may be stimulated. After bilateral vagotomy, parasympathomimetic drugs, with the exception of Group 2, may be expected to stimulate both secretion and motility. Drugs of Group 2 may stimulate secretion slightly and diminish emptying markedly if the stomach has been freed of vagal influence.

EXAMPLES OF GASTRIC RESPONSE TO PARASYMPATHOMIMETIC DRUGS AFTER VAGOTOMY

In order to show the effect of several different autonomic agents on gastric secretion and emptying data obtained from a single patient are shown in Table 2. The method used for obtaining these data is outlined briefly on page 31. The subject was a sixty-four year old colored male with a history of duodenal ulcer disease for twenty years and who had experienced several bouts of complete gastric obstruction during the one year preceding surgical treatment of his ulcer and retention. On August 29, 1946, a transabdominal bilateral vagotomy and anterior gastroenterostomy were performed.* All symptoms were relieved immediately following surgery and none have recurred. Three satisfactory insulin tests have been performed after vagotomy and all have been negative. The last one was performed twenty five months postoperatively.

In demonstrating the effect of parasympathomimetic agents on gastric function, there are several reasons for presenting data from a person with vagotomy. First, these agents have been and are being used to relieve gastric retention which has occurred in some persons following vagotomy. Secondly, the effect of these drugs may be more pronounced after vagotomy because of the stimulation of gastric activity which they produce in a stomach which has been relatively quiet. Finally, the paradoxical response to prostigmine after vagotomy, as contrasted with the response to other parasympathomimetic agents may be used to illustrate the different mechanism of action of these different types of drugs.

* Surgery was performed by Dr. R. Arnold Griswold, University of Louisville, Louisville, Kentucky.

Table 2 Gastric Response after Vagotomy

PERIOD*	DURATION	SECRETORY RATE	EMPTYING RATE	VOLUME INJECTED†	pH‡	PEPTIC POWER‡	FREE ACIDITY‡	REMARKS
	MINUTES	CC PER MIN	CC PER MIN	CC	UNITS	UNITS	CLIN UNITS	
12/12/46								
1	13 0	4 95	3 93	50	4 69	170	0 0	
2	13 5	2 83	3 29	50	4 60	190	0 0	
3	15 5	2 45	1 96	50	5 08	180	0 0	
4	14 5	3 46	1 66	50	3 03	700	0 9	*Subcut doryl 0 25 mg*
5	14 0	4 12	8 07	50	1 77	1560	17 0	
6	13 5	3 97	6 13	50	1 17	1260	68 0	
7	13 0	3 86	5 29	50	1 88	1010	13 0	
8	13 0	3 09	3 74	50	1 51	970	31 0	
7/17/47								
1	14 0	0 74	1 85	50	6 75	650	0 0	Oral doryl 8 6 mg retained § 20 mg in 200 cc saline solution was injected through gastric tube at start of period #4 11 4 mg was recovered with complete aspiration of gastric contents at end of period 4
2	15 5	1 36	2 79	50	6 91	935	0 0	
3	15 0	0 58	2 35	50	4 66	815	0 0	
4	22 0	2 35	5 70	200	2 96	790	1 1	
5	15 0	2 94	4 95	50	2 62	920	2 4	
6	16 5	3 18	5 80	50	2 11	1100	7 8	
7	16 0	3 12	5 63	50	2 51	990	3 1	
8	16 0	2 93	5 42	50	3 15	490	0 7	
3/5/47								
1	14 5	2 72	5 78	100	5 18	100	0 0	
2	18 5	2 44	2 00	100	6 15	0	0 0	
3	16 5	1 75	3 08	100	6 29	0	0 0	
4	16 0	2 06	6 56	100	7 00	0	0 0	Subcut urecholine 5 0 mg
5	15 5	3 81	6 78	100	6 12	3	0 0	
6	15 0	3 24	3 30	100	5 00	230	0 0	
7	17 0	2 01	1 09	100	4 13	635	0 0	
8	14 5	3 34	2 86	100	4 45	400	0 0	
6/25/47								
1	14 0	1 52	0 31	50	4 44	680	0 0	Oral urecholine 9 2 mg retained § 20 mg in 200 cc saline solution was injected through gastric tube at start of period #4 11 8 mg was recovered with complete aspiration of gastric contents at end of period #4
2	14 0	1 77	2 98	50	6 39	0	0 0	
3	20 0	0 79	1 45	50	3 49	510	0 0	
4	27 0	0 84	4 24	200	5 28	135	0 0	
5	16 0	1 21	1 16	50	5 49	170	0 0	
6	16 5	1 78	2 91	50	6 21	0	0 0	
7	17 5	1 08	2 26	50	3 46	360	0 4	
8	14 0	1 53	2 67	50	6 09	0	0 0	
12/18/46								
1	15 5	3 43	1 74	50	3 75	132	0 0	
2	14 0	1 52	2 45	50	2 09	39[illegible]	8 2	
3	13 0	2 05	1.30	50	3 28	225	0 5	
4	14 5	3 17	0 00	50	3 22	173	0 6	I M prostigmine 0 5 mg
5	13 0	3 00	0 00	50	2 58	437	2 6	
6	12 5	4 66	2 02	50	2 53	500	3 0	
7	13 0	3 25	2 11	50	2 46	620	3 5	
8	12 0	3 12	1 03	50	2 04	530	9 0	

See opposite page for footnotes

Table 2 shows that doryl and urecholine, orally and parenterally, were followed by an increase in secretory and emptying rates Acidity was increased by doryl but was slightly affected by urecholine, even though the subcutaneous dosage of the latter drug was twenty times the dosage of doryl Peptic activity was increased by the subcutaneous administration of each drug, particularly doryl, but was little affected by the oral administration of either A comparison of doryl with urecholine shows that the former produced approximately the same degree of influence on secretory and emptying rates when administered subcutaneously in but one-twentieth the dosage of urecholine A comparison of responses following the oral administration of approximately equal retained§ dosages shows that doryl was about two and a half times more effective than urecholine in stimulating secretion and emptying It is of interest to note that the effect produced by the subcutaneous administration was equal to or greater than the effect following much larger oral dosages This difference of magnitude of effect produced by the two routes of administration was not due to retention of the drug in the stomach which may have prevented absorption, because, as already pointed out the retained dosages were those which were emptied through the pylorus (retained within the body) within twenty five minutes after the oral administration of 20 mg of drug

The side effects produced in these instances were of no consequence Subcutaneous urecholine produced a slight increase in perspiration There was neither urination nor defecation during any of the test periods The maximum increase of average salivary secretion for a fifteen minute period over the control values is as follows oral doryl—4 ×, oral urecholine—1½ × subcutaneous doryl—2½ ×, and subcutaneous urecholine—2½ ×

These responses to doryl and urecholine are representative for these two drugs when administered to a person with bilateral vagotomy As mentioned previously the responses elicited in a person without vagotomy may not be so pronounced because the percentage change from the control is not so great as the percentage change produced after vagotomy, even though the preoperative peak values for response may be and usually are higher

The gastric response to prostigmine is similar to that of doryl and urecholine, providing the parasympathetic innervation of the stomach is intact The reason for this as already stated is that the anti-cholinesterase property

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* Periods 1 2 and 3 are controls About three minutes elapsed between periods

† 'Volume injected is the volume of isotonic saline containing phenol red (test meal) which was injected into the empty stomach at the beginning of each period Other factors remaining unchanged gastric emptying rate is approximately proportional to the volume injected

‡ Values of pH peptic power and free acidity are for the gastric juice contained in the aspirated contents These recorded values were calculated from the aspirated specimens by correcting the latter for dilution by the test meal pH determinations were made with Beckman pH meter free acidity values were calculated from pH readings and peptic powers were determined by a modification of method of Mett

§ Retained refers to that portion of drug which was injected into the stomach at the start of the period and which was not recovered by aspiration at the end of the period It applies to the quantity of drug retained by the body

of prostigmine permits acetylcholine, which is continuously liberated from nerve endings, to act more intensely and for a longer period of time However, if the parasympathetic innervation of the stomach is disrupted by bilateral vagotomy, then the response to prostigmine is, in many ways, opposite to the preoperative response This reversal of influence of prostigmine in the presence of vagotomy is due to a combination of two factors These factors are (1) the absence of acetylcholine at the effector cells of the stomach because of the interrupted vagal (parasympathetic) supply, and (2) the presence of an intact sympathetic nerve supply to the stomach, the postganglionic fibers of which are stimulated at the peripheral ganglia through the action of prostigmine The net result is the stimulation of the stomach by the sympathetic nervous system Since the stimulation of the sympathetic nerves to the stomach produces a gastric response which is, with exception, antagonistic to parasympathetic stimulation, then the effect of prostigmine on a vagotomized stomach is opposite to its effect on a stomach with intact nerve supply The exception to this concept is that while sympathetic stimulation inhibits gastric motility, in contrast to the increase in motility produced by parasympathetic influence, the sympathetic nerves stimulate the flow of neutral secretions without inhibiting the secretion of acid or pepsin

The table shows the effect of prostigmine on gastric function, and demonstrates the various "paradoxical responses produced by this parasympathomimetic agent after bilateral vagotomy It shows quite clearly that the secretory rate was increased and that there was very little, if any, increase in acidity This suggests that, contrary to parasympathetic stimulation which would produce acid gastric juice, the increased volume secreted was of neutral reaction This is further supported by the fact that there was a concurrent increase in the peptic activity of the gastric juice which would also represent an increase in neutral secretion The marked reduction in the rate of gastric emptying, in this instance a complete abolition of emptying for at least twenty seven and a half minutes immediately following injection of the drug, is in contradistinction to the effect of parasympathetic stimulation The inhibitory effect of prostigmine on gastric emptying in the presence of vagotomy may be explained as a result of sympathetic stimulation at the peripheral (celiac) ganglion through the anti-cholinesterase action of prostigmine, thereby causing a reduction in gastric motility and emptying

The gastric response to prostigmine after vagotomy is of considerable clinical importance For example, in the period immediately following bilateral vagotomy, it is not unusual for gastric retention to produce bothersome symptoms in those persons in whom a concomitant low gastroenterostomy was not performed Since such a condition usually subsides spontaneously after several weeks or months, it may be treated palliatively by the use of gastric stimulants Inasmuch as vagal denervation produces retention by creating a relaxed and immotile stomach, the rational means for treating this side effect is by use of parasympathomimetic agents which stimulate gastric function Since for a number of years it has been the practice of many to use prostigmine to stimulate intestinal peristalsis, there has been a tendency to

employ this same drug to stimulate gastric peristalsis after vagotomy From theoretical considerations as well as from practical experience, it is obvious that prostigmine not only fails to stimulate gastric motility after bilateral vagotomy, but it may, and usually does, diminish any motility which may have been present before the drug was administered The example cited from the data of the table is evidence of this response to prostigmine after vagotomy On the other hand, parasympathomimetic agents which are included in Groups 1 and 3 are very effective as gastric stimulants whether the vagal trunks are intact or have been severed Therefore it may be stated briefly that the drugs of Groups 1 and 3 will stimulate gastric secretion and emptying before and after vagotomy, and the drugs of Group 2 will produce a similar response before vagotomy but will inhibit emptying after vagotomy

SUMMARY AND CONCLUSIONS

1 Parasympathomimetic drugs have been defined by Dale as those autonomic drugs which act upon structures that are innervated by cholinergic nerves Cholinergic nerves include all preganglionic nerves of the autonomic system, the postganglionic nerves of the parasympathetic system and the somatic motor nerves to skeletal muscle

2 Except for the anti cholinesterases and those drugs which stimulate sympathetic ganglion cells, all other parasympathomimetic drugs act independently of nerve function

3 Anti-cholinesterases, acetylcholine doryl and mecholyl are parasympathomimetic drugs which, through stimulation of sympathetic ganglia, may produce sympathomimetic effects

4 Parasympathomimetic drugs will stimulate secretion, emptying acidity and peptic activity in a stomach with intact nerve supply providing the stomach is capable of secreting and contracting in response to a stimulus If the gastric mucosa is atrophic, there may be no secretory response

5 After bilateral vagotomy all parasympathomimetic drugs, except the anti cholinesterases, produce a gastric response similar to the preoperative response to the same drugs After vagotomy the anti-cholinesterases produce a paradoxical response i e, they inhibit motor activity and do not appreciably stimulate secretory rate or acidity Because of this paradoxical response prostigmine, which is popularly used to stimulate intestinal peristalsis, should not be used after bilateral vagotomy for the purpose of stimulating gastric emptying

of prostigmine permits acetylcholine, which is continuously liberated from nerve endings, to act more intensely and for a longer period of time However, if the parasympathetic innervation of the stomach is disrupted by bilateral vagotomy, then the response to prostigmine is, in many ways, opposite to the preoperative response This reversal of influence of prostigmine in the presence of vagotomy is due to a combination of two factors These factors are (1) the absence of acetylcholine at the effector cells of the stomach because of the interrupted vagal (parasympathetic) supply, and (2) the presence of an intact sympathetic nerve supply to the stomach, the postganglionic fibers of which are stimulated at the peripheral ganglia through the action of prostigmine The net result is the stimulation of the stomach by the sympathetic nervous system Since the stimulation of the sympathetic nerves to the stomach produces a gastric response which is, with exception, antagonistic to parasympathetic stimulation, then the effect of prostigmine on a vagotomized *stomach is opposite to its effect on a stomach with intact nerve supply* The exception to this concept is that while sympathetic stimulation inhibits gastric motility, in contrast to the increase in motility produced by parasympathetic influence, the sympathetic nerves stimulate the flow of neutral secretions without inhibiting the secretion of acid or pepsin

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of hydrochloric acid was decreased in all instances (average 75 per cent), largely as a result of the decrease in volume

Side Effects Mydriasis, cycloplegia and dryness of the mouth were experienced by all subjects given the drug Paralysis of accommodation was not always complete and usually lasted two to four hours, somewhat longer than the effect on gastric secretion

Comparison with Atropine Three of our subjects given a subcutaneous injection of 2 mg of atropine had an average diminution in volume of secretion of 68 per cent This closely approximates our results with dibutoline The duration of action of atropine was approximately forty five minutes longer than that of dibutoline, averaging one hundred and thirty three minutes

We concluded from these studies that dibutoline in doses of 30 to 60 mg produces a marked decrease in the volume of interdigestive gastric secretion—approximately 75 per cent for ninety minutes Although the effects on titra

Table 3 Effect of Dibutoline on Volume and Acidity of Gastric Secretion

NUMBER OF SUBJECTS	DOSE IN MG	DURATION DIMINISHED SECRETION IN MINS	ABOLITION OF SECRETION IN MINS	PERCENTAGE DEPRESSION OF GASTRIC SECRETION	EFFECT ON FREE ACIDITY D	I	N
4	30	122	45	76	4	0	0
15	40	89	11	77	5	4	6
3	50	93	27	82	2	0	1
3	60	93	27	62	1	1	1

D = decreased I = increased N = no change

table acidity are not consistent the reduction in volume of secretion accounts for a considerable decrease in the total output of hydrochloric acid The equal effectiveness of atropine over a longer period is somewhat offset by its greater toxicity, especially as a stimulant of the central nervous system

EFFECTS OF DIBUTOLINE WITH HISTAMINE AND INSULIN

We next turned our attention to the effect of dibutoline on the gastric secretory response to stimulation with histamine and insulin Our results, although few in number would indicate that dibutoline, like atropine, will partially inhibit the response to these stimuli

In Fig 14 are represented secretory responses to 0 3 mg of histamine and 0 3 mg of histamine plus 40 mg of dibutoline The values are expressed in mg HCl which is calculated by multiplying volume times concentration It can be seen that a partial inhibition of secretion is produced by the drug (66 per cent)

INHIBITION OF GASTRIC SECRETION IN ULCER PATIENTS WITH DIBUTOLINE

STANLEY H. LORBER, M.D.

A drug that will effectively inhibit nocturnal gastric secretion should be a useful adjunct in the therapy of peptic ulcer and some of its complications. I should like to report the results of studies on the effect of dibutoline (dibutyl urethane of dimethyl-ethyl-β-hydroxyethyl ammonium sulfate) on gastric secretion of patients with peptic ulcer.

A number of choline esters were prepared by Swan and White[1] in 1944. They found that certain derivatives, rather than possessing a parasympathomimetic action, apparently compete physiologically with acetylcholine normally present in the body, and thus behave as parasympatholytic drugs. Dibutoline appears to be the most promising member of this group.

Investigations have shown[1-6] that dibutoline will produce mydriasis and cycloplegia. The drug depresses gastrointestinal motility[7-9] and has been reported to be an effective spasmolytic agent in a variety of conditions.[10] Marquardt et al.[11] were able to produce partial inhibition of histamine stimulated gastric secretion in dogs following the subcutaneous administration of 10 mg. doses of the drug. They also gave similar doses to 5 patients with ulcer and noted either a depression or complete suppression of acid secretion for periods not exceeding one hour.

Dr. Machella and I[1] first studied the action of dibutoline on interdigestive gastric secretion of ulcer patients. After collecting fasting gastric secretions for control periods of forty to sixty minutes, the drug was administered subcutaneously in doses of 10 to 60 mg. and samples of gastric contents were collected for ten minute periods until the rate of secretion approximated that of the basal period.

GENERAL EFFECTS OF DIBUTOLINE

1. *Volume.* Dibutoline, when administered subcutaneously in doses of 30 to 60 mg., produced a marked diminution in the volume of gastric secretion (Table 3). This effect usually occurred within three to ten minutes after injection and lasted as long as two hundred and twenty minutes. The period of inhibition was not increased by the use of doses greater than 30 mg., and the same was true for the decreases in volume. The drug appeared to inhibit gastric secretion completely in 18 of 25 experiments during one or more ten minute collection periods. The longest period of apparent complete suppression of gastric secretion was seventy minutes.

Acidity. Unlike the rate of secretion titratable gastric acidity was not consistently altered by the drug (Table 3). In 12 instances acidity was decreased, in 5 it increased, while in 8 no significant change occurred. The total output

In Fig 15 are represented secretory responses to insulin (20 units administered intravenously), and insulin plus 40 mg of dibutoline, the latter given subcutaneously It can be seen that the drug partially inhibits (64 per cent) the secretory response resulting from hypoglycemia

EFFECTS ON NOCTURNAL GASTRIC SECRETION

Many investigators have observed that gastric acid is secreted continuously throughout the night In all studies but one, patients with duodenal ulcer were found to have higher acidity and greater volume of gastric secretion than

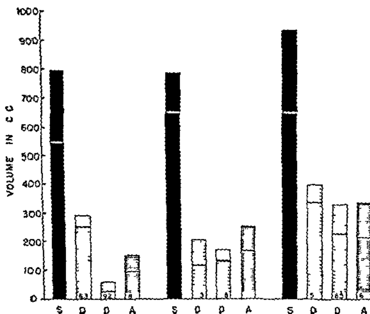


Fig 16 Volumes of gastric night secretion in three subjects S = Average of 2 control nights D = 40 mg of dibutoline administered every four hours D = 40 mg of dibutoline administered every three hours A = 1 mg atropine administered every three hours The break in each column divides the volume for the first three hours of secretion (lower)

normals At the present time we are investigating the effects of dibutoline and atropine on night secretion of patients with uncomplicated duodenal ulcers Subjects are admitted to the hospital for a period of six days during which time they are given a bland diet with frequent feedings between 7 A M and 4 P.M daily At 6 45 P M a Levin tube is introduced into the gastric antrum under fluoroscopic observation and the gastric residuum is evacuated Continuous aspiration is maintained for twelve hours and the aspirate is collected hourly On successive nights subjects receive subcutaneous injections at three hour intervals of (1) 3 cc saline (2) 40 mg dibutoline, (3) 1 mg atropine sulfate, (4) 3 cc saline On the fifth night 40 mg of dibutoline is given every four hours No other medication is allowed during the period of hospitalization except vitamins and possibly a mild laxative in the morning

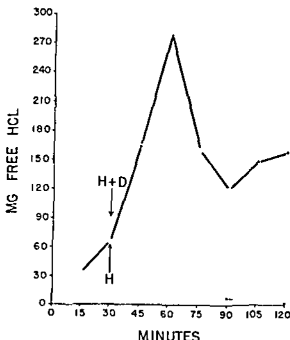


Fig 14 Partial inhibition of gastric secretory response to histamine H (solid line) represents the response to 0 3 mg of histamine administered subcutaneously H + D represents the response to the simultaneous subcutaneous administration of 0 3 mg of histamine and 40 mg of dibutoline Total acid output was decreased 66 per cent by dibutoline

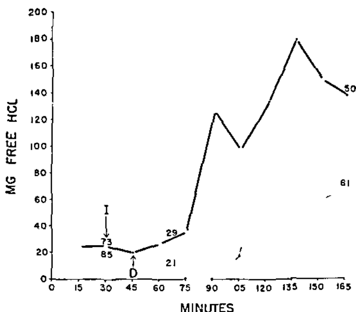


Fig 15 Partial inhibition of gastric secretory response to insulin I (solid line) represents the response to 20 units of insulin administered intravenously D (broken line) represents the response to the same dose of insulin plus 40 mg of dibutoline the latter administered subcutaneously fifteen minutes later Numbers above the lines represent blood sugar determinations showing that hypoglycemia ensued Total acid output was decreased 64 per cent by dibutoline

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12 Lorber S H and Machella T E In press

SECRETION OF GASTRIC MUCUS IN HEALTH AND DISEASE

FRANKLIN HOLLANDER, PH D

DR BOCKUS *We are very fortunate that Dr Hollander has been kind enough to come down here from New York and tell us something of his investigations with gastric mucin in health and in disease*

DR HOLLANDER

EARLIER STUDIES OF MUCIGOGUE ACTION

In an article published in the American Journal of Medical Sciences in 1908, Dr Kaufman of New York[8] presented what he thought was a new clinical entity which he designated as 'gastric amyxorrhea It was his concept that the mucosa of many patients who are suffering from the usual symptoms of ulcer disease without having any manifest ulcer, shows a deficiency, not in mucous secretion but in the mucus stimulating mechanism As a result the mucosa has inadequate protection of its epithelial cell layer This in turn makes it possible for the acid—which is normally present in these patients particularly since many of them are hypersecretors—to act even more vigorously on the underlying nerve endings than it would if there were an adequate layer of this protective mucous secretion Kaufman cited evidence for this concept, based on the secretory response to a tea and toast test meal, and he reported results on the treatment of several hundred patients with very dilute solutions of silver nitrate (0 02 to 0 1 per cent) as a mucigogue The results were very encouraging to Kaufman, but unfortunately he neglected to consider the fact that 0 1 per cent silver nitrate contains only about 6 milliequivalents per liter, and a solution of that low concentration of silver nitrate would have all of its silver completely precipitated by the

Although determinations have been made of pH, acidity, chlorides and pepsin, the most striking change observed is in volume of secretion Studies on the volume of secretion of three subjects are represented in Fig 16 The control figures illustrate the average secretion of two nights Both dibutoline and atropine produce a marked decrease in the volume of secretion in these cases Dibutoline given every four hours is less effective than when given every three hours Atropine is slightly less effective than dibutoline but the differences are not significant—78 per cent reduction as compared with 71 per cent Dibutoline *given every fourth hour decreases secretion 64 per cent* Hourly specimens have been obtained on all control nights In the first two subjects, the third hour injections of dibutoline produced complete suppression of secretion for five hours

SIDE EFFECTS

Dryness of the mouth was the only *symptom complained of when dibutoline* was administered When atropine was given this same symptom was so dis turbing that the patients requested that the treatments be discontinued Irritability, dizziness and restlessness were also quite marked following the administration of atropine

SUMMARY

The following inferences may be drawn from these data

(1) Dibutoline is as effective as atropine in inhibiting gastric secretion

(2) Dibutoline is shorter acting than atropine but after repeated doses at three-hour intervals is equally effective

(3) Night secretion in ulcer patients can be greatly inhibited by the administration of either dibutoline or atropine

(4) Side effects produced by atropine are more severe and more numerous It does have the advantage, however, of being effective by mouth

(5) Dibutoline should prove useful in controlling night secretion of peptic ulcer patients

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DR HOLLANDER

EARLIER STUDIES OF MUCIGOGUE ACTION

In an article published in the American Journal of Medical Sciences in 1908, Dr Kaufman of New York[8] presented what he thought was a new clinical entity which he designated as gastric amyxorrhea It was his concept that the mucosa of many patients, who are suffering from the usual symptoms of ulcer disease without having any manifest ulcer, shows a deficiency, not in mucous secretion, but in the mucus-stimulating mechanism As a result, the mucosa has inadequate protection of its epithelial cell layer This in turn makes it possible for the acid—which is normally present in these patients particularly since many of them are hypersecretors—to act even more vigorously on the underlying nerve endings than it would if there were an adequate layer of this protective mucous secretion Kaufman cited evidence for this concept, based on the secretory response to a tea and toast test meal, and he reported results on the treatment of several hundred patients with very dilute solutions of silver nitrate (0 02 to 0 1 per cent) as a mucigogue The results were very encouraging to Kaufman, but unfortunately he neglected to consider the fact that 0 1 per cent silver nitrate contains only about 6 milliequivalents per liter, and a solution of that low concentration of silver nitrate would have all of its silver completely precipitated by the

chloride, both acid and neutral, which is normally present in the stomach In other words, the mucigogue action of the silver must have been destroyed immediately and completely before it could be effective This report is typical of the kind of reasoning that we so often encounter in relation to ulcer disease in the stomach and duodenum, where spontaneous remissions of symptoms are often ascribed to the influence of a therapeutic agent

Other stimulating agents have been proposed for clinical purposes For instance, there is a preparation of silver tannate (targesin) which was brought from abroad and used in this country by Dr Harris Levy of Syracuse I do not know that he reported his clinical results with this mucigogue at any time Malo reported the use of histidine for the purpose either of stimulating secretion or, more likely, of inducing increased formation of mucus in the gastric mucosa, and he recommended its use in relation to ulcer therapy specifically Meyerson, Rinkel and associates recommended the use of mecholyl as a parasympathomimetic agent which would stimulate mucus output through a nontopical mechanism Ivy and his associates reported some work on the use of hydrogen peroxide in animals as a very mild mucigogue, and even more recently, Meyer and Necheles reported their results with a clinical application of oil of peppermint for its mucigogue action

The term, gastric amyxorrhea, was never adopted seriously, but the underlying idea seems to have persisted in one way or another throughout these fifty years We still find the general belief among gastroenterologists that a layer of mucous secretion on the surface of the mucosa affords a vital protective mechanism against autodigestion by acid and pepsin in the stomach, and also against bacterial, chemical, thermal and mechanical irritants of various types More recently, another term has crept into the literature—"gastric myxasthenia This term is also not commonly used, but its proposal indicates that the essential idea has persisted, even though there is as yet very little physiologic evidence to substantiate it It is interesting that none of these physiologic reports concerning various types of mucus stimuli has ever been followed up clinically I may say that we also are working with such an agent, and like our predecessors, we also get marked symptomatic improvement in many of our patients, but the changes are hardly of such a nature as to prove a real therapeutic effect, or to indicate that the increased output of mucus is *actually the effective factor This does not mean that mucous* secretion is not important so far as gastric disease is concerned, but rather that there are many aspects of this problem—both clinical and physiologic—which still require clarification

Another approach to the problem, of course, is related to the use of hog mucin given orally The rationale of this therapy, in part, is the administration of an antacid substance, and there is no doubt that hog mucin is effective in this regard It also was believed by Fogelson and others who worked with it that this preparation forms a layer on the surface of the mucosa and thereby exercises mechanical protective action just like native mucus, but how important this is has never been demonstrated

THE PHYSIOLOGY OF GASTRIC MUCUS

In view of such uncertainty on the subject, I decided some years ago that it was time we got down to basic work on the physiology of this most important protective device which operates throughout the whole length of the gastrointestinal tract We must forget the utilitarian clinical problem for the time being and learn something about its physical and chemical characteristics, and some of the physiologic mechanisms involved in its elaboration and secretion For these purposes, we set out to study the effects of a number of different chemical agents which could be applied topically to the gastric mucosa We used Heidenhain pouch dogs in the fasting state, in order to minimize the amounts of acid and pepsin secretion which were mixed with



Fig 17 Exp CA 75-8 Control tissue Residual stomach—no eugenol application (100× reduced one fourth from original photograph)

the mucus The mucigogue was placed inside the pouch for varying lengths of time and under varying conditions Originally[6] we studied changes in the chemical and physical characteristics of the nonacid secretion, but more recently we started a study of the changes in the tissue itself which are con comitant with the changes in the secretion Much of our work has been performed with a 5 per cent aqueous emulsion of eugenol as the mucigogue This chemical compound is the chief component of oil of cloves, and has been employed consistently in all our recent work for reasons which have been stated in our published reports [4]

It must be generally known to you that the outstanding physical characteristics of mucus are its high viscosity, its tenacity and particularly its high surface tension activity Figure 17 is a section of gastric mucosa from a dog s pouch Essentially the pouch was in a resting condition without acid secre-

tion, at the time the animal was sacrificed and tissue taken for sectioning I simply want to call your attention here to the fact that although the layer of mucus which covers the surface of this tissue is very thin, it adheres to this surface very tenaciously Even where the mucus has been forced away from the tissue mechanically, *it still clings to the columnar epithelium in some* spots The viscosity of such mucus also tends to be extremely high, but it may vary over a considerable range Sometimes the material has the consistency merely of a viscous fluid, but at other times it is thick as jelly or egg white

Figure 18 is a section of tissue from an animal, taken at autopsy thirty minutes after the application of eugenol to the interior of the pouch Through out this half-hour period, the amount of mucus which was pouring out of the



Fig 18 Exp CA 76-1 Initial fatigue series Pouch tissue—twenty nine minutes after first eugenol application (100 X reduced one fourth from original photograph)

pouch was really large—many times that which was secreted spontaneously before application of the mucigogue Notice how it continues to adhere to the mucosa, both within the fold and on the surface, in spite of all of the mechanical factors which operated on this tissue between the time the animal was killed and when the section was prepared This is clearly a consequence of *its high viscosity as well as its cohesiveness and tenacity* Observe also the large cell content of this mucus, which was not apparent in the previous section of spontaneous secretion I ll tell you more about this very shortly It is obvious that with a layer of a highly viscous secretion *of this kind*, the glandular epithelium of the stomach wall is protected by a most efficient mechanism which we have designated the ' mucous barrier of the stomach This term includes not only the layer of mucus itself but also the columnar mucous epithelium which lies above the collecting gland tubules Why we

include the latter in the protective mucous barrier you will learn from what I shall have to say about the desquamatory response of the gastric mucosa to topical irritants simultaneous with their mucigogue action

CHEMICAL CONSTITUENTS

What about the chemistry of the secretion? Its chief chemical constituent is a complex organic compound called *mucin* We believe it to be a mucoprotein comprising a globulin and a complex polysaccharide The composition of this polysaccharide which is probably a polymer of large molecular weight, was described years ago by P A Levine as consisting of two molecules of glucuronic acid two of glucosamine, two of acetic acid and two of sulfuric acid The polymerized form of course, would contain these four substances

Table 4 Variations in Calcium Concentration in Gastric Mucus and Blood Serum (Dogs)

EXP NO	NO OF MUCUS SPECIMENS	MUCUS CALCIUM (mg /100 ml)		SERUM CALCIUM (mg /100 ml)	DIFFERENCE
		RANGE	MEAN		
300	8	8 4–10 1	9 0	10 6	1 6
303	8	9 3–10 4	10 1	11 0	0 9
305	7	9 7–10 6	10 1	11 5	1 4
306	7	9 7–10 6	9 9	11 7	1 8
307	8	8 3–11 2	10 3	12 3	2 0
308	9	9 1–11 3	10 3	11 8	1 5
Grand Mean	—	—	10 0	11 5	1 5

in the same proportion More recently, there has been some reason for questioning the exact arrangement of these components in the molecule, but that matter is still far from having been decided I should mention that there are at least two different mucins in gastric juice—one soluble and the other insoluble—and only one of these contains the sulfuric acid It may very well be that one of these is related to the true mucous secretion from the surface cells of the gland and the other to the so called mucoid secretion The latter may be formed by these same cells on the surface of the mucosa or by the low columnar epithelium which lies lower down in the crypts, at the present time there is no clear cut evidence on this point

The inorganic cations which are normally present in gastric juice are primarily sodium and potassium as you would expect to find in any of the exo-

crine secretions of the digestive tract, but curiously enough, the mixed secretion also has a fairly high concentration of *calcium* As a result of some of our earlier investigations on gastric hydrochloric acid, there is good reason to believe that these ions are derived solely from the nonacid secretions of the stomach Because calcium may be important in relation to the physical properties of mucus, we determined the variations in concentration of this element which may occur ordinarily under the influence of eugenol or mustard oil in Heidenhain pouch dogs [3] The data in Table 4 indicate a mean calcium concentration of about 10 mg per 100 ml of mucous secretion For comparison, we collected blood from these same dogs at the same time that the experiments were being performed Notice that mean serum calcium was a little bit higher than the mucus calcium—11 5 as compared with 10 0 mg per 100 ml That this difference is significant is suggested by the fact that the serum calcium is higher than the mucus calcium in every one of these six groups of experiments It seems very probable to me that this high calcium content may be related to the colloidal properties of the secretion, particularly its viscosity and tenacity Its presence may also have something to do with the loosening of the cement substance, which almost always accompanies mucigogue action [9]

Data on *chloride* concentration showed very extensive variations Much to our surprise, we found values varying from 57 to 186 millinormal,[1] with a mean of 122 mN We thought that these chloride values would always be markedly lower than in the acid secretion, where they run about 150 to 160 mN Such a wide range of variation in mucus chloride concentration may be correlated with variations in bicarbonate or other anion values—much as in pancreatic secretion These other anions are known to be present, although they have not been studied quantitatively as yet

HYDROGEN ION CONCENTRATION

It is the pH, however, which is particularly interesting, and not only in connection with the presence of the bicarbonate and phosphate [7] Figure 19 shows a frequency distribution for the pH values of almost 600 specimens of gastric mucus collected from these pouch dogs under a variety of experimental conditions Notice that there are few values below pH 6 8—somewhat less than 15 per cent of the total It seems likely that these low values result from the admixture of very minute amounts of hydrochloric acid though we have never been able to prove this positively Above pH 7, however, the frequency rises very sharply to a peak at 8 5 The pH range goes up as high as 9 2 in other words, mucus secreted spontaneously in the resting stomach, or mucus which was formed by stimulation with topical mucigogues, may have an alkaline pH as high as 9 This value, I believe, is the highest pH which has been encountered anywhere in the mammalian body Sometimes pancreatic juice may reach a pH of this value, but never above it It is interesting that the stomach may give the highest pH found anywhere in the body, as well as the lowest From these data, therefore, we are led to believe that mucus is distinctly an alkaline substance, if we define alkalinity solely in

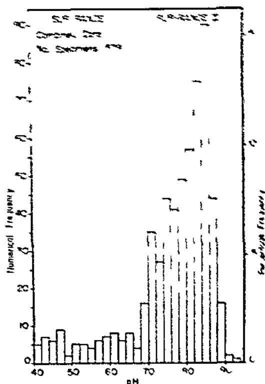


Fig 19 Frequency distribution for pH values of gastric mucous secretion from Heidenhain pouches (combined data—all stimuli)

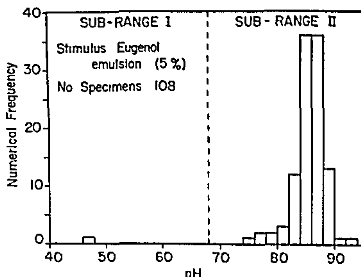


Fig 20 Frequency distribution for pH values of gastric mucous secretion from Heidenhain pouches (after stimulation of mucosa with 5 per cent eugenol emulsion)

terms of the pH In terms of acid-neutralizing power (*i e*, *buffer capacity*), however, this may not always be the case—as we shall see shortly

Since eugenol is the mucigogue most frequently used in our work, let us examine the pH data for specimens of mucus collected with a 5 per cent emulsion of this agent (Fig 20) This frequency graph represents 108 such specimens out of the 579 in Fig 19 Notice how the pH values concentrate around the upper part of the range—much more than they do for the samples collected with the other agents It was for this reason that we thought eugenol a more effective stimulus than any of the others that we investigated, and subsequently adopted it as a standard stimulus for our current investigations

Now, since we are interested in the way in which mucus is formed inside the cells, it naturally occurred to us that this alkaline substance must lose some of its carbon dioxide immediately after it is secreted by the cell, and

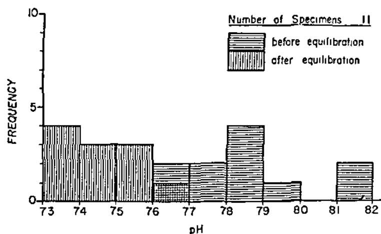


Fig 21

particularly during the time that it is exposed to air on the surface of the gastric mucosa Therefore, we took several samples of the secretion and equilibrated them with alveolar air—just as is done in determining the CO_2 combining power of blood For the latter purpose, it is possible to minimize the loss of CO_2 by collecting the sample under oil and to equilibrate the sample of whole blood or serum or plasma with alveolar air in order to adjust its carbon dioxide content to the CO_2 tension in the alveoli For mucus studies, only the second of these steps is possible Figure 21 is a frequency graph for 11 samples of blood or its derivatives that were treated in this way The pH values in these experiments ran initially from 7 6 to 8 2 Following equilibration, all of these came down to the range from 7 3 to 7 6—values that we ordinarily accept as characteristic of normal blood under various physiologic conditions We therefore applied this same equilibration technic to our

mucus specimens,[5] and found that the very high pH s are characteristic of mucus only after it has been extruded from the cell and exposed to the air for some time (Fig 22) All of these specimens which, before equilibration, had pH s of 7 9 to 8 9, came down to the range 7 3 to 7 8 as a result of this treat-

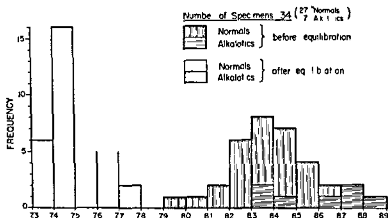


Fig 22

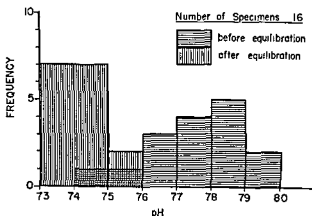


Fig 23

ment The value of this upper limit is higher than is ordinarily obtained in blood or plasma, and when we encountered it, we were somewhat puzzled We therefore checked the blood pH s of our animals shortly after collection of the mucus (i e the same day) and found that these values also ran a little

high In other words, the dogs were in a temporary state of mild alkalosis In this way we were able to account for the unexpectedly high pH values, even after calibration, and were fairly well convinced that mucus as it is formed in the cells has a pH identical with that of blood and tissue fluids in general A similar set of data on the mucoid secretion collected with a 1 per cent emulsion *of mustard oil (Fig 23) serves to confirm this conclusion*

BUFFER CAPACITY

We also have some data on the buffer capacity of mucus, which was determined by electrometric titrations of 0 5 ml samples to an end point of pH 3 5 These titers fell between 10 and 85 millinormal, with an average of about 35 millinormal, which means that 100 ml of mucus, of the type collected in these experiments, will neutralize 35 ml of tenth normal hydrochloric acid, on the average I am struck by the fact that this is a moderate but not extremely high buffering power Our evidence that the pH of the material as it is formed in the cell is about the same as for blood or serum, and not higher, is also significant, and together these observations lead me to believe that perhaps gastric mucus may not play as important a role as an antacid in the stomach as we have believed Whether it does or not must depend also on the rate of secretion, i e , the volume per unit time, under ordinary conditions of digestion and rest, but these remain to be determined in subsequent studies

CELLULAR CONTENT AND DESQUAMATION

What about the microscopic appearance of the mucus? Sometimes smears of mucus collected in such experiments are transparent and contain no intact cells, though they may show some cellular debris, such as can be seen in Fig 24 The little threads are coagulated mucin or possibly material of slightly higher viscosity than that in the surrounding areas Occasionally it has been possible to collect specimens entirely free even of such cellular debris, as illustrated in Fig 25, but this is not a common occurrence What happens much more frequently is that the mucus collected in such experiments is full of columnar and other cells, in a more or less intact condition Interestingly enough, we sometimes find parietal cells and neck chief cells in this material also, but not in great number Peptic cells are never present That may be not because they are not shed, as a rule, but because they are destroyed following desquamation The desquamated columnar cells occur not only as single cells, but in small groups, ranks or palisades, groups as large as the one in Fig 26 are not at all uncommon The cells of this particular specimen lost their mucus before they were shed, but sometimes one can see a rank of cells which still retain their thecae full of metachromatic mucus They look very much like goblet cells of the intestinal epithelium though it is questionable whether there are any such cells in the gastric mucus

This desquamating action is almost invariably associated with topical mucigogue activity Nevertheless, these two functions of mild chemical irritants are probably independent of each other, because mucus secretion can

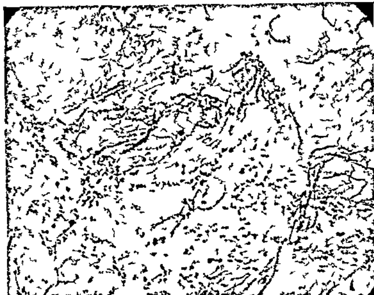


Fig 24 Smear of non-opaque viscous gastric mucus obtained with NaCl (0 5 N) as stimulus (Wright s stain 75× reduced one fourth from original photograph) Cellular debris but no intact cells

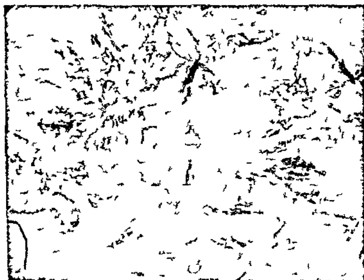


Fig 25 Smear of non opaque viscous gastric mucus (toluidine blue 75× reduced one fourth from original photograph) No suspended material

also occur entirely unaccompanied by the *shedding of columnar epithelium* Our observations suggest that the latter is a consequence of a secondary, but independent, chemical action whereby the eugenol or other agent loosens the



Fig 26 Smear of opaque gastric mucus of heterogeneous viscosity (Wright s *675× reduced one fourth from original photograph) Large rank or palisade of* columnar cells



Fig 27 Exp CA 75-8 Control tissue Residual stomach—no eugenol application (100× reduced one fourth from original photograph)

cement substance of the mucosal surface and thus permits the cells on that surface to be separated from it and mixed with the viscous mucus

How readily can the desquamated epithelium be replaced under ordinary laboratory conditions? In more or less normal gastric pouch tissue, which has

not been subjected to any eugenol treatment whatever (Fig 27) the density of the crypts per unit length of section is essentially the same as in normal human gastric tissue Half an hour after eugenol application, however, the density of the crypts is greatly diminished A striking illustration of this is seen in Fig 28, where there occurs a stretch of mucosal surface in which the crypts have been lost almost entirely Sometimes we find a layer of mucus free flat cells covering such denuded areas within two hours following treatment with eugenol emulsion The character and source of these cells are matters which we do not have time to go into today, but they are of the utmost importance in connection with this rapid regeneration of the columnar epithelium In any case, we have here visual evidence of the vigor of the desquamation and the amazing rapidity with which the reparative process occurs The strip



Fig 28 Exp 64–5 Initial fatigue series Pouch tissue—twenty seven minutes after third eugenol application (100× reduced one fourth from original photograph)

of mucus which is adherent to the mucosa contains many of these cells, singly and in groups as well as several long lines of the epithelium which had been ripped off in the course of this experiment

Two hours after the seventh of a series of such pouch applications of eugenol which were made at about two and a *half* hour intervals, the animal was killed and tissue specimens taken for study It is evident from the section illustrated in Fig 29 that the crypts had been disrupted entirely in the course of this experiment and the process may have extended even into the necks of the gland tubules The amount of denudation which occurred in these experiments as a result of such repetitive treatment with the mucigogue is really tremendous I grant you that the conditions here were not such as are encountered ordinarily in clinical situations but it may well be that after a protracted bout of alcohol drinking or of overeating—especially of highly

spiced foods—this sort of thing takes place in considerable degree even in the normal human stomach



Fig 29 Exp CA 68-1 Initial fatigue series Pouch tissue—one hundred and twenty minutes after seventh eugenol application (100× reduced one fourth from original photograph)



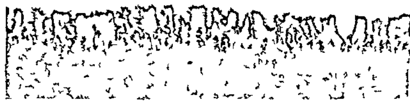


Fig 30 Exp CA 69-1 Recovery period Pouch tissue—thirty six and a half hours following initial fatigue series (100× reduced one fourth from original photograph)

The last illustration (Fig 30) however, shows what happens thirty six hours after such complete denudation There is an almost complete regeneration of the crypts of the mucosa, which confirms the other evidence that the

rate of resurfacing of the mucosa is extremely rapid, and that it begins well within one hour after denudation has occurred This rapid rate of repair accounts for the chronic character of the lesions of peptic ulcer disease—especially when the reparative process alternates repeatedly with an equally rapid process of localized autodigestion by active gastric juice

This is a very rapid review of work on the physiology of mucus secretion that we have been doing in our laboratory in the course of the last five years What the results mean for our clinical problems, we cannot tell yet We are well convinced that these phenomena are significant in relation to ulcer disease and its attendant symptoms and to gastric hypersecretion and distress in general, but they may also have a bearing on the etiology of gastric adeno carcinoma There is a very definite possibility that the intact mucous barrier protects the underlying glandular epithelium against topically applied carcinogens in experimental animals, and we are at present carrying on a series of experiments along with our physiologic studies to evaluate the importance of this in the development of an adenocarcinoma in rodents following the ingestion of carcinogenic hydrocarbons

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RATIONALE OF THE USE OF VARIOUS GASTRIC ANALYSIS PROCEDURES IN THE STUDY OF GASTRIC FUNCTION AND DISEASE

JAMES L d'A ROTH, PH D , M D

The rational use of gastric analysis in the study of gastric secretory function and of the effects of diseases upon it presupposes a working knowledge of the mechanisms of gastric secretion and the factors that regulate the acidity of the gastric contents A brief review[1] of this subject may be approached by outlining the periods and stages of gastric secretion These divisions are artificial and for the purposes of analysis It is understood that the phases of digestive secretion may overlap and occur simultaneously

INTERDIGESTIVE GASTRIC SECRETION

Gastric secretion may be divided into two periods (a) the interdigestive period and (b) the period of digestive secretion The *interdigestive secretion*[2] is that which occurs in the absence of food in the stomach and intestines The appearance of hydrochloric acid in the gastric juice of the interdigestive period is intermittent and not continuous Unless it is recognized that the empty stomach does secrete periodically, the fortuitous occurrence of the spontaneous secretion after the introduction of an experimental procedure may be erroneously interpreted as evidence of stimulation Therefore, in experimental work on man or animal, the interdigestive secretion should be collected for a period before any procedure is introduced, and the fact should be kept in mind that a small increase may be spontaneous The cause for the intermittent secretion of hydrochloric acid during the interdigestive period is unknown However, the following theoretical possibilities have been proposed (1) It has been attributed to the psychic influence, this may be partially true but vagotomy does not abolish it (2) Alterations in the blood flow of the gastric glands have been suggested (3) Some correlation has been noted between hunger contractions and spontaneous secretion (4) It has been attributed to digestion of gastric detritus, or (5) the intermittent release of the small amount of a gastric hormone

There is some evidence that the mechanism of the interdigestive secretion may be disturbed in the patient with peptic ulcer, i e , the interdigestive secretion of hydrochloric acid in peptic ulcer patients is usually substantially above the normal average The exposure of the gastroduodenal mucosa to excessive secretions when acid neutralization and pepsin inactivation by food and alkaline secretions are at a minimum may be an important factor in ulcerogenesis This has given rise to the "night secretion test which is currently being used in various clinics to test the physiologic effectiveness of vagotomy It is supposed to determine the neural component of the secretion

stimulating mechanisms However, it would appear that the high interdigestive secretion in ulcer patients cannot be entirely attributed to the neural mechanism Although the volume of secretion is usually reduced by relatively large doses of atropine in the ulcer patient, the secretion is not abolished by this drug as is the normal interdigestive secretion This suggests that in such patients some abnormal process is concerned, or that some process which plays a minor role in a normal state has been activated It is possible that histamine is being produced excessively by an irritated mucosa, since the secretory response to histamine is not completely abolished by large doses of atropine, doses in the neighborhood of 1 to 2 mg

DIGESTIVE GASTRIC SECRETION

The *period of digestive secretion* refers to the response to a meal This period is divided into three phases the cephalic the gastric and the intestinal, the name denoting the region in which the stimuli are acting to stimulate gastric secretion The *cephalic phase* is provoked by stimuli such as the thought, smell, sight and taste of food These stimuli act in the presence of appetite through either conditioned (learned) or unconditioned reflexes the former are dependent upon the integrity of the cerebrum and the latter are not The vagi are the principal efferent nerves of the cephalic phase Section of the vagi or large doses of atropine will abolish this phase

The gastric juice of the cephalic phase is highly acid and possesses considerable peptic activity The amount of juice secreted during the cephalic phase in man is extremely variable The volume of secretion is affected by appetite the attitude of the patient the agreeableness of the food, the time consumed in its ingestion, especially in the process of mastication, and the manner in which the food is prepared Lack of uniformity in the methods used by the various investigators has also contributed to the wide variations in the values for the cephalic phase However the intravenous administration of insulin promises to provide more reproducible data for estimating the secretory potentiality of the cephalic phase The insulin test will be discussed later

In the *gastric phase* the stimuli are acting in the stomach Two types of stimulating agents when applied to the stomach excite the parietal cells to secrete They are (a) mechanical distention and (b) secretagogues Grossman and Ivy[3] have recently demonstrated the humoral transmission of the *distention* stimulus In a two pouch dog distention of the pyloric portion of the stomach stimulates the secretion of hydrochloric acid by the fundic glands This effect still occurs when all nervous connections between the stimulated portions of the stomach and the portion responding to secretion have been interrupted Such interruption can be accomplished by the subcutaneous transplantation of either that part of the stomach which is to be stimulated i e, the pyloric portion or that part which responds to stimulus the fundic portion This demonstration of the humoral transmission of the distention stimulus is considered conclusive evidence of the existence of a hormone for gastric secretion

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Gastric secretion may be divided into two periods (a) the interdigestive period and (b) the period of digestive secretion The *interdigestive secretion* is that which occurs in the absence of food in the stomach and intestines The appearance of hydrochloric acid in the gastric juice of the interdigestive period is intermittent and not continuous Unless it is recognized that the empty stomach does secrete periodically, the fortuitous occurrence of the spontaneous secretion after the introduction of an experimental procedure may be erroneously interpreted as evidence of stimulation Therefore, in experimental work on man or animal, the interdigestive secretion should be collected for a period before any procedure is introduced, and the fact should be kept in mind that a small increase may be spontaneous The cause for the intermittent secretion of hydrochloric acid during the interdigestive period is unknown However, the following theoretical possibilities have been proposed (1) It has been attributed to the psychic influence, this may be partially true but vagotomy does not abolish it (2) Alterations in the blood flow of the gastric glands have been suggested (3) Some correlation has been noted between hunger contractions and spontaneous secretion (4) It has been attributed to digestion of gastric detritus, or (5) the intermittent release of the small amount of a gastric hormone

There is some evidence that the mechanism of the interdigestive secretion may be disturbed in the patient with peptic ulcer, i e, the interdigestive secretion of hydrochloric acid in peptic ulcer patients is usually substantially above the normal average The exposure of the gastroduodenal mucosa to excessive secretions when acid neutralization and pepsin inactivation by food and alkaline secretions are at a minimum may be an important factor in ulcerogenesis This has given rise to the 'night secretion test which is currently being used in various clinics to test the physiologic effectiveness of vagotomy It is supposed to determine the neural component of the secretion

psychic phase after completion of the meal, the gastric phase as the stomach empties, etc The influence of variations in gastric evacuation upon gastric acidity is obvious If the withdrawal of stimuli does not check an inordinate rise in acid concentration the so-called self regulatory mechanisms are called into play namely, acid inhibition and enterogastric regurgitation of alkaline intestinal contents *Inhibition of gastric secretion may be neural or humoral in mechanism* Both the vagi and splanchnics contain inhibitory fibers and mental states may inhibit gastric secretion through these pathways *Distention* of the intestine also inhibits gastric secretion and this may take place reflexly The vagi are essential to inhibition of pepsin secretion following the instillation of fat in the intestine Acid inhibition results from the presence of acid in the stomach or intestine, but whether or not it occurs depends upon the nature and potency of the stimulus It appears to be due to a nervous rather than a humoral mechanism When neutral fats or sugars are placed in the upper small intestine in sufficient concentration (10 per cent or higher), both gastric motility and gastric secretion are markedly depressed Since this *inhibition has been demonstrated to occur in a subcutaneously transplanted* gastric pouch the effect has been attributed to a humoral mechanism Ivy has shown that such inhibition is due to the release of a chalone named enterogastrone which is capable of suppressing gastric secretion stimulated by a meal, sham feeding histamine or insulin Consideration of these inhibitory influences has clinical importance For example if one fails to consider psychic inhibition coincident to swallowing the tube and aspirates gastric contents only thirty and sixty minutes after the test meal, the mistaken *diagnosis of apparent achlorhydria might result* whereas if a fractional analysis were carried out for two hours or more, a delayed secretion curve may then be demonstrated Grossman and Ivy[8] have also observed that nausea and retching inhibit histamine stimulated gastric secretion in dogs with denervated transplanted pouches They conclude that the mechanism of this phenomenon is either vascular or hormonal in nature

The rise and fall in acid concentration of the gastric juice itself is due to the changing proportion of parietal to nonparietal secretion Most of the water in gastric juice is secreted by the parietal cell *Therefore the acid concentration* of mixed juice varies directly with the volume rate of secretion When the rate of parietal secretion is low either at the beginning or end of stimulation, the parietal secretion represents a smaller fraction of the mixed gastric juice and the acidity is thus lowered The amount of visible mucus secretion in *response to a meal will* depend upon the amount of stimulation which the surface epithelial cells receive from chemical and mechanical irritants Thus, a rough or spicy diet will enhance mucus production Mucoid (soluble) secretion of the gastric glands is probably controlled mainly by vagal reflex some of which may be local in character involving postganglionic neurones within the gastric wall In general the mucus and soluble mucoid secretion contribute only a small part to the total volume of gastric secretion and the variation of the secretory rate between the digestive and interdigestive periods is not nearly so great as in the case of parietal cell secretion *The chief enzyme*

Secretagogues are chemical substances of two types (1) those which are naturally present in food, e g, the extractives of lean meat, the whey of milk and liver, and (2) those which arise from the digestion of food, such as the split products of protein digestion and possibly fatty acids In an animal provided with both an extrinsically denervated transplanted pouch and a pouch in the remainder of the stomach, perfusion of the main pouch with a secretagogue preparation causes the transplant to secrete Similarly, on feeding a two pouch dog with an esophagoduodenostomy, the transplant will secrete Thus, a humoral mechanism is involved in the action of secretagogues in the stomach or in the intestines

The pyloric mucosa contributes to, but is not the sole origin of, the humoral agent arising in the stomach The humoral agent may be (1) histamine, (2) a hormone other than histamine, which may or may not be histamine-like, or (3) secretagogues, absorbed unchanged or acted upon first by the digestive secretion Mechanical distention and secretagogues may theoretically act (a) by stimulating a local sensory receptor mechanism which may excite an intermediate nerve or substance acting upon the parietal cell by a secretory or vasomotor intrinsic reflex, or (b) by releasing a hormone which stimulates parietal cell secretion Atropine abolishes the secretory response to a meal, but not to alcohol, histamine or caffeine The evidence indicates that alcohol stimulates the parietal cell through the release of histamine If histamine is a normal humoral agent, then alcohol releases histamine by a different mechanism from that concerned in the release of histamine by secretagogues in food This other mechanism is presumed to be irritation

The gastric stage has previously been considered to be independent of the vagus However, Stein and Meyer[4] have recently reported a marked decrease in the secretory response to histamine or caffeine following complete vagotomy in man Grossman[5] has suggested that the responsiveness of the gastric glands to all types of stimuli may be dependent upon the basal level of acetylcholine production in the stomach, and thus upon the vagus activity This would explain the decreased action of secretagogues following vagotomy

In the *intestinal phase* the only type of stimuli which excite gastric secretion are secretagogues elaborated in the intestine Mild distention has no effect, undue distention or irritation of the intestine at first inhibits gastric secretion, presumably reflexly Further injury to the intestinal mucosa may produce stimulation by releasing histamine

FACTOPS AFFECTING GASTRIC ACIDITY

Inasmuch as we measure the acidity of the gastric contents in clinical gastric analyses and not pure parietal cell secretion it is essential to consider the factors which regulate that acidity Whereas the pure parietal secretion has an acidity of 159 mEq per liter the actual acidity of the gastric contents is so regulated by the following processes that it rarely exceeds 50 to 60 mEq per liter in normal individuals After the dilution and neutralization caused by the meal are ended, the acidity of the gastric contents rises However, it does not rise too high because the stimuli for secretion are withdrawn the

gastritis and by Hurst to a constitutional deficiency The incidence of achlorhydria increases with advancing age and thus probably represents an accentuation of the physiological involution About 25 per cent of persons sixty years of age and above have achlorhydria with the histamine test and 35 per cent with an Ewald meal Achlorhydria is a common finding in microcytic hypochromic anemia and an almost constant finding in primary pernicious anemia *Hydrochloric acid facilitates iron absorption, but this cannot be the only factor* inasmuch as only one third of the patients with true achlorhydria manifest anemia Other conditions with an associated true achlorhydria include gastrogenous diarrhea, a syndrome of postepigastric distress simulating peptic ulcer longstanding ulcerative colitis and gastritis True achylia gastrica or the absence of both hydrochloric acid and enzymes, is not often found in cases of gastric carcinoma, although achlorhydria is present in more than 50 per cent of patients with this disease However, it is important to remember that any degree of acidity may be associated with carcinoma of the stomach. The finding of true achylia gastrica with low total acidity after histamine points more toward an achylia associated with pernicious anemia than toward the diagnosis of carcinoma or even gastritis

CAFFEINE TEST OF GASTRIC SECRETION

Caffeine is a potent gastric stimulant Inasmuch as bilateral vagotomy, large doses of atropine and procaine lavage of the denervated stomach do not abolish stimulation [8] it would appear *that caffeine, like histamine,* predominantly acts peripherally on the gastric glandular mechanisms The resistance of caffeine stimulation to atropine is analogous to that of alcohol and of histamine stimulation of gastric secretion The evidence indicates that *alcohol, which stimulates when given by any route stimulates gastric secretion* by causing a release of histamine However, several observations are inconsistent with this analogy when carried out with caffeine

Caffeine has the unusual property of potentiating the gastric secretory response to stimulants such as alcohol and histamine[9] thus the acid output in response to histamine plus caffeine is greater than the sum of the responses to these stimulants administered singly The response to the combined action of these drugs is prolonged and maintained at a high level If caffeine acts by a histaminergic mechanism, how then could we explain the caffeine histamine synergism? Doubling a dose of histamine which yields a response equal to that of caffeine does not result in a sustained increase in the output of hydrochloric acid like that obtained from caffeine and histamine given simultaneously Caffeine juice is similar to histamine juice with regard to *pepsin concentration* *i e*, the pepsin response to histamine or caffeine is of low magnitude in comparison with the insulin or vagal secretion [10] This is indirect evidence that the nervous mechanism of gastric secretion is not to any great extent involved in the stimulation of gastric secretion by caffeine However the pepsin output in normal subjects is sustained *longer than the* response to histamine The prolonged increase in the pepsin output and con

of the gastric juice is the proteolytic principle pepsin, which is secreted by the body chief cells of the fundic glands Vagus nerve stimulation, insulin hypoglycemia and parasympathomimetic drugs are all potent stimulants of pepsin secretion The role of other humoral and hormonal factors in the control of pepsin secretion has not been fully investigated

Having considered the mechanisms of gastric secretion and the factors that regulate the acidity of the gastric contents, let us now direct our attention to several of the more commonly used procedures for testing gastric secretory function In the limited time available today, it is possible to discuss only the following histamine, caffeine and insulin tests and the fractional analysis of Rehfuss using a carbohydrate meal I d like to discuss these tests from the point of view of the rationale for their use, limitations and the information that may be gained from them

HISTAMINE TEST OF GASTRIC SECRETION

Histamine is the most potent stimulant known for the parietal cell The secretagogue effect of histamine is humoral and not nervous in origin, and consequently its secretion is not at all or only partly inhibited by atropine or vagotomy One mg of atropine subcutaneously in dog or man produces a definite but limited inhibition in the response to histamine The inhibition consists chiefly of a decreased volume output, the acid concentration remains unchanged or may even rise, probably due to the inhibition of the nonparietal secretion Histamine acts principally and directly upon the parietal cell It also increases the output of pepsin from the chief cells so that the concentration of pepsin is relatively low compared to vagal stimulation Histamine is not an ideal substance for the maximum stimulation of other secretory elements in the stomach, such as enzymes and mucin The histamine test performed without the simultaneous ingestion of the Ewald meal will supply no information concerning the motor function of the stomach

The principal value of the histamine test is in the differentiation of true from apparent *achlorhydria* or *achylia* May I remind you that achlorhydria is the absence of free hydrochloric acid, and achylia the absence of both hydrochloric acid and the enzyme pepsin If no free acid is found in the course of the fractional gastric analysis, the test should be repeated using histamine before a diagnosis of true achlorhydria is made Bockus[7] has found that 64 per cent of persons who secreted no free acid in response to the Ewald meal did respond to histamine In patients who have been observed continuously over a long period of years during which they were developing achlorhydria, the usual sequence of events was hypochlorhydria apparent achlorhydria, apparent achylia, true achlorhydria and finally true achylia Thus, pepsin almost invariably persists for some time after hydrochloric acid secretion can no longer be stimulated Histamine causes pepsin to be secreted in many stomachs long after hydrochloric acid secretion has ceased, in spite of the claim of certain physiologists that histamine does not stimulate pepsin secretion

The cause of achlorhydria is unknown It has been attributed by Faber to

patients than in his normal control subjects This he interpreted as evidence for a hyperirritable vagus nucleus in patients with duodenal ulcer as compared with normal subjects Thus, the insulin test may serve as a measure of psychic secretory or vagal irritability, but further investigation along this line is needed

Some of the important features of the technic and interpretation of the insulin test have been summarized recently by Hollander[14] as follows

(a) The purpose of the test is to determine whether any functionally effective secretory nerves continue to pass to the stomach after vagotomy, and possibly to serve as a measure of psychic secretory or vagal irritability

(b) Two successive samples of resting gastric secretion should be aspirated at fifteen minute intervals in addition to emptying the fasting contents The resting acidity provides a more valid base line for gauging the postinjection rise of the acidity curve Insulin dosage alone or physical signs of hypoglycemia cannot be used as evidence of an adequate hypoglycemia in place of the blood sugar curve Clinical studies have indicated empirically that a blood sugar level of 50 mg per 100 cc is adequate for vagal stimulation in most instances If there is no significant rise in the free acidity curve with a minimum blood sugar above 50 mg per 100 cc, the test must be declared invalid and repeated

(c) A positive response is indicated by a well defined rise in the free acidity curve following injection i e two or more points must be distinctly above the base line one of which should be 20 mN or more A positive response after a bilateral vagotomy indicates the persistence of some secretory nerves, either truly vagal or vagomimetic of spinal origin It does not imply of necessity, that the surgeon failed to interrupt the gastric vagi completely

(d) A negative response is defined by an acidity curve which is either flat or shows a downward slope without a subsequent rise in a patient who is capable of secreting hydrochloric acid as shown by the histamine test, or some other test A negative response indicates a neurectomy has been achieved, provided a postoperative achlorhydria is ruled out with histamine and that a neutralization anacidity can be excluded

CARBOHYDRATE TEST MEAL

The *fractional gastric analysis of Rehfuss* using some form of carbohydrate as a test meal is still the most commonly used procedure in the study of gastric function, and probably should be It provides a crude but more complete measure of the stomach s work not only its secretory capacity, but also its motor functions The gastric secretory response to a meal depends upon the quantity and chemical nature of the food and the relish with which it is eaten All mechanisms of stimulation may, to some extent, be called into play, that is vagal, mechanical and secretagogue hormonal or otherwise Water stimulates secretion by its psychic effect by hydremia, distention and facilitation of digestion and absorption Protein in itself does not stimulate, but the products of protein digestion are good secretagogues In addition, the water soluble extractives of protein food are potent secretory excitants

centration after caffeine is also incompatible with the 'histaminergic mechanism' for caffeine stimulation

The failure of atropine to abolish the high interdigestive secretion in duodenal ulcer patients has been taken as evidence that histamine, or some histamine like substance, may be responsible for part of this secretion A histamine cycle has been suggested in which the irritated mucosa liberates histamine which in turn stimulates gastric secretion, the action of the gastric juice on the ulcer liberates more histamine, and thus the cycle continues If histamine is being released from the irritated mucosa of the ulcer patient, then the administration of caffeine alone should provoke a sustained synergistic response similar to that observed in normal subjects given both caffeine and histamine This is precisely what has been observed[11] The majority of patients with active "peptic' ulcer disease respond to the caffeine test meal with a prolonged and sustained stimulation of the total output of free hydro chloric acid The majority of normal subjects, however, respond to caffeine with an abrupt transient stimulation with a peak followed by a return to normal control level within sixty to seventy minutes However, in a small group of asymptomatic and otherwise normal medical students, the prolonged secretory response was obtained An upper gastrointestinal study revealed no evidence of gastroduodenal ulcer at the time of the caffeine gastric analyses In the follow-up period of six months to two years, 4 out of 5 of this group developed symptoms and roentgenologic evidence of peptic ulcer disease Whether or not the caffeine tests will prove to have diagnostic or prognostic value remains to be demonstrated by its continued use on a large scale

INSULIN TEST OF GASTRIC SECRETION

Insulin has been shown to provoke the secretion of gastric juice by hypoglycemia, the latter acting in part upon the vagal center The response to insulin was originally considered a test for the continuity of the vagi However, more recent evidence indicates that there may be some secretory nerves contained in the cervical vagi which reach the stomach via channels other than the main gastric trunks, for example, those which course within the esophageal wall or those which branch off from the esophageal trunks to pass through the diaphragm independently Also cholinergic nerves[12] arise in the thoracic segments of the spinal cord and pass through the celiac plexus to the stomach There is some likelihood that these spinal nerves contain gastric secretory as well as motor fibers and it is entirely likely that like the vagi such vagomimetic nerves would also be susceptible to hypoglycemic stimulation Hence, until evidence to the contrary has been obtained, the insulin tests must be considered in relation to all gastric secretory nerves and not restricted to the gastric vagi alone

To elucidate the pathologic physiology of gastric secretion in ulcer disease and in view of the possibility that ulcer is ultimately a psychosomatic disorder, Winkelstein[13] recently undertook his study of insulin hypoglycemia to study the cephalic or vagus phase of gastric secretion in ulcer patients He found that even smaller drops in blood sugar evoked a higher acid response in ulcer

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SOME FALLACIES IN THE CLINICAL MEASUREMENT OF GASTRIC SECRETION WITH SPECIAL REFERENCE TO THE HISTAMINE TEST

HARRY SHAY, M D

There is a distinct need for reexamination of methods and definition of terms as used in clinical medicine to measure gastric acidity I am aware that the requirements of the clinician often do not have to be as rigid as those set down in the physiologic laboratory nevertheless, I think it behooves us as clinicians to be just as exacting and as accurate in the definitions of terms employed in clinical medicine In this connection I would like to discuss the

Starches are not secretagogues, their stimulating action is due to psychic secretion and distention Sugars and fats act similarly, except that in concentrations above 10 per cent they elicit enterogastrone formation with the inhibition of secretion and motility The carbohydrate test meal (bread and water, oatmeal gruel, etc) possesses an advantage over more potent secretagogues such as liver extract or bouillon Often a stomach may exhibit an average acidity after a carbohydrate meal, but a hyperacid response to alcohol or meat extracts, so that a differentiation between a normal secreting stomach and a hypersecretory stomach of duodenal ulcer cannot be made using a protein meal

As previously implied, there are a number of factors that can influence the concentration of gastric acidity, viz , dilution by swallowed saliva, entero gastric regurgitation of alkaline duodenal contents, differences in the rate of emptying, acid inhibition, withdrawal of stimulation, etc Because of these variables different types of secretory responses have been obtained If there is an absence of duodenal regurgitation, a reduction in alkaline nonparietal secretion or prolongation of the gastric secretory activity beyond the accepted normal time, the so-called "extra-gastric curve' or a continually rising secretory curve is obtained In the delayed secretion curve," hydrochloric acid may or may not be present in the fasting residuum, and after the introduction of a test meal with its neutralizing effect, there may be no further appearance of hydrochloric acid until sixty to seventy minutes or more have elapsed after the ingestion of the meal This response may be due to failure of the cephalic phase of gastric secretion or intolerance to the tube with psychic inhibition After the subject is ' tube broken, the normal curve may be obtained Classification of the degree of hyperacidity is useful in the appraisal of the duodenal ulcer patient The more profound the hyperacidity, experience has demonstrated, the more likely it is a gastrojejunal ulcer will develop after subtotal resection

Information relative to the stomach's motor function is of great clinical importance Emptying as reflected by the fractional analysis method is more physiologic and more representative of the stomach s emptying behavior with ordinary food than a barium meal emptying time The quantity and character of the overnight fasting residuum may indicate impairment of the stomach s emptying function If an excessive volume is recorded, it may be due to gastric motor delay, but if there is food sediment also present there is some interference, either functional or organic in the emptying power of the stomach If an excess food sediment is recovered in the two-hour extraction, this is indicative of some delay in stomach emptying The efficiency of chymification is likewise reflected in the sediment of the two hour extraction An appraisal of motor function may be useful in the follow up management of duodenal ulcer For example, the diet is not materially increased as long as abnormal emptying of the stomach persists Time does not permit a description of the technic for the fractional analysis but I d like to emphasize the importance of following the proper technic to gain the most information from this procedure [15]

gastric samples were anacid to Topfer s reagent pH of each sample was determined with a Beckman pH meter and glass electrode with a micro attachment In addition, total chlorides were measured by the method of Wilson and Ball in most instances, and pepsin concentration by Nierenstein s modification of the Mett method pepsin activity was determined with Mett tubes in the unaltered samples of gastric contents The titration figures in all the figures represent free hydrochloric acid titrated with Topfer s reagent and total acidity titrated with phenol red as indicators

The routine test meal used was 30 gm of zwieback and 300 cc of water and the usual fractional analysis was done in all cases When no free acid was obtained with the test meal, a similar meal was given on a subsequent day and histamine phosphate (0 25 mg in a 1 1000 acqueous solution) was injected subcutaneously when the test meal was started The first two fifteen-minute extractions were spot tested with Topfer s reagent and if no free acid was found, a second injection of histamine phosphate (0 5 mg) was given subcutaneously

RESULTS

Let us consider Fig 31 The absence of free hydrochloric acid in this case was definitely established by both titration and pH determinations pH was on the alkaline side in both tests with and without histamine Note how

P IENT			F	5	30	45	60	5	90	05	20
1/5/ EWALD ME L	C D TY (meq/)	FREE	0	0	0	0	0	0	0	0	0
		TOTAL	0	0	0	0	0	0	0	0	0
	pH		857	832	828	830	830	821	805	791	753
	E S (Uni)	CONC	0	0	0	0	0	0	0	0	0
		ACT	0	0	0	0	0	0	0	0	0
	Cl (meq/)		NOT DONE								
/8/ 8 E ELO SAMPLE ITH R 30 AF MG H	ACIDI (me /)	FREE	0	0	0	0	0				
		TOT L	0	0	0	0	0		-		
	pH		808	740	713	711	735				-
	PE S (Uni)	CONC	NOT DO E								
		CT									
	Cl (me /l)		55	19	11	16	27	-	-	-	-

MIN TES			F	5	30	45	60	75	90	05	20
3/ 2/		FREE	0	0	0	0	0	0	0	0	0
		TOTAL	0	0	0	0	0	0	0	0	0
	pH		795	735	782	771	781	808	795	819	808
		CONC	0	0	0	0	0	0	+	+	QNS
		ACT	QNS								
	Cl		NO E								
3/5 7		FREE	0	0	0	0	0	0	0	0	
		TOT L	0	0	0	0	0	0	0	0	
	pH		782	778	798	775	763	78	727	788	
		CONC	0	0	0	0	02	05	08	010	
		CT	0	0	0	0	0	0	0	0	
	Cl		NO DO E								

Fig 31

similar was the gastric response obtained in this individual at approximately ten month intervals

In Fig 32 please note that while no free titratable acidity was present in any sample of gastric contents total acid could be titrated in the last four specimens, which of course was to be expected, since the pH was between 3 94 and 4 76—well on the acid side After histamine stimulation both free and total acidity could be titrated—again in agreement with the pH values obtained

In Fig 33 you will also see no free titratable acidity some titratable total

question of so-called 'anacidity' and the validity of gastric acid measurements upon which the diagnosis of this condition is based

INDICATORS AND METHODS

In relation to titratable acidity, let us consider first the question of indicators The accepted titration end point for the determination of free hydrochloric acid in a gastric sample is pH 3 5 At this hydrogen ion concentration there is still present about one milliequivalent of free acid Dimethyl aminoazobenzene (Topfer s reagent) is the indicator most frequently employed May I point out that the proper end point at pH 3 5 for this indicator is orange and not yellow When titration is carried to the yellow color, the pH is 4 5 or higher We have repeatedly checked the proper end point for pH 3 5 with Topfer s reagent by electrometric titration Many years ago Dr Hollander recognized the desirability of a more accurate end point in titrating free hydrochloric acid and recommended that bromphenol blue be used We have continued to use Topfer s reagent for a reason that you will see in a moment

The usual procedure in titrating for total acidity is to employ phenol phthalein as an indicator Here too, the proper end point for titration needs reconsideration The question may well be asked What is the objective in titrating beyond the point of practically complete neutralization of free hydrochloric acid? Actually one could conceive of titrating to different end points depending upon the information desired Thus in a patient with a peptic ulcer we might be interested in the titration figure of the gastric contents to pH 5 0, the proteolytic neutralization point—the pH at which all peptic digestion stops Were we interested in determining the amount of alkali to be added to produce neutrality physicochemically, then one should titrate to pH 7 0 On the other hand, if we are concerned with measuring total acidity, then for reasons which I shall point out later, titration to the proper end point for phenolphthalein at pH 8 5 is probably best

For titration to pH 7 0 phenol red serves as a very satisfactory indicator This indicator gives a yellow color at hydrogen ion concentrations below 7 0, orange at 7 0 and red at pH above 7 0 Hollander has recommended the use of bromphenol blue as an indicator when titrating for free hydrochloric *acid and phenol red for titration to physicochemical neutrality* We have used Topfer s reagent to the end point as described above plus phenol red, because it is then necessary for the technician to retain visual memory for only one series of color changes from the red of Topfer s reagent at pH below 3 5 to the orange at pH 3 5, through the yellow for Topfer s reagent at a pH above 3 5 and for phenol red in the pH range below 7 0, then again to orange for phenol red at pH 7 0

In our experience when free hydrochloric acid is present in the gastric contents, titration of the free acid is satisfactory It is only when no free acid is present, as shown by the yellow color after the addition *of Topfer s reagent,* that the interpretation of gastric acidity as measured by titration and our classification of those results come into question In our studies, when the

gastric samples were anacid to Topfer s reagent pH of each sample was determined with a Beckman pH meter and glass electrode with a micro attachment In addition total chlorides were measured by the method of Wilson and Ball in most instances, and pepsin concentration by Nierenstein s modification of the Mett method pepsin activity was determined with Mett tubes in the unaltered samples of gastric contents The titration figures in all the figures represent free hydrochloric acid titrated with Topfer s reagent and total acidity titrated with phenol red as indicators

The routine test meal used was 30 gm of zwieback and 300 cc of water and the usual fractional analysis was done in all cases When no free acid was obtained with the test meal a similar meal was given on a subsequent day and histamine phosphate (0 25 mg in a 1 1000 acqueous solution) was injected subcutaneously when the test meal was started The first two fifteen minute extractions were spot tested with Topfer s reagent and if no free acid was found a second injection of histamine phosphate (0 5 mg) was given subcutaneously

RESULTS

Let us consider Fig 31 The absence of free hydrochloric acid in this case was definitely established by both titration and pH determinations pH was on the alkaline side in both tests with and without histamine Note how

PATIENT J P	MINUTES F	15	30	5	60	75	90	05	20
EWALD MEAL — ACIDITY FREE	0	0	0	0	0	0	0	0	0
EWALD MEAL — ACIDITY TOTAL	0	0	0	0	0	0	0	0	0
EWALD MEAL — pH	857	832	828	830	830	821	805	791	753
EWALD MEAL — PEPSIN CONC	0	0	0	0	0	0	0	0	0
EWALD MEAL — PEPSIN ACT	0	0	0	0	0	0	0	0	0
EWALD MEAL — Cl (meq/l)	NOT DONE								
HISTAMINE WITH MEAL — ACIDITY FREE	0	0	0	0	0				
HISTAMINE WITH MEAL — ACIDITY TOTAL	0	0	0	0	0				
HISTAMINE WITH MEAL — pH	808	740	713	711	735				-
HISTAMINE WITH MEAL — PEPSIN CONC	NOT DONE								
HISTAMINE WITH MEAL — PEPSIN ACT									
HISTAMINE WITH MEAL — Cl (meq/l)	55	19	11	16	27				

	MINUTES F	5	30	5	6	75	90	05	20
3/22/ — ACIDITY FREE	0	0	0	0	0	0	0	0	0
3/22/ — ACIDITY TOTAL	0	0	0	0	0	0	0	0	0
3/22/ — pH	795	735	782	771	781	808	735	819	808
3/22/ — PEPSIN CONC	0	0	0	0	0	0	+	+	QNS
3/22/ — PEPSIN ACT	QNS								
3/22/ — Cl	O DONE								
3/31/ — ACIDITY FREE	0	0	0	0	0	0	0	0	
3/31/ — ACIDITY TOTAL	0	0	0	0	0	0	0	0	
3/31/ — pH	78	776	798	775	763	782	727	768	
3/31/ — PEPSIN CONC	0	0	0	0	02	05	08	010	
3/31/ — PEPSIN ACT	0	0	0	0	0	0	0	0	
3/31/ — Cl	O DONE								

Fig 31

similar was the gastric response obtained in this individual at approximately ten month intervals

In Fig 32 please note that while no free titratable acidity was present in any sample of gastric contents total acid could be titrated in the last four specimens which of course was to be expected since the pH was between 3 94 and 4 76—well on the acid side After histamine stimulation both free and total acidity could be titrated—again in agreement with the pH values obtained

In Fig 33 you will also see no free titratable acidity, some titratable total

patient should be considered in the category of one failing to secrete hydro chloric acid in response to histamine

Figure 35 represents another example of failure to obtain titratable evidence of parietal cell stimulation by histamine, although it was clearly indicated by pH measurement

These examples can be multiplied many times—all showing conclusively that titration alone very often does not provide sufficient information and that pH measurements are of *great value in deciding whether or not a true anacid* ity is present The difficult question that must be decided, however, is At what level of pH can we be certain that there has been no secretion of hydro chloric acid, and what decrease in pH in the gastric contents after histamine would represent unquestionable evidence of acid secretion?

PATIENT - D N			MINUTES F	15	30	45	60	75
1/31/47 EWALD MEAL	ACIDITY (m eq/l)	FREE	0	0	0	0	0	0
		TOTAL	0	05	25	25	4	6
	pH		71	69	67	61	57	56
	PEPSIN (Mett U)	CONC	+	+	40	31	41	31
		ACT	0	0	0	0	+	QNS
	Cl (meq/l)		NOT DONE					
1/28/47 HISTAMINE PHOSPHATE 025 MG WITH MEAL 05 MG AFTER 30 MIN SAMPLE	ACIDITY (meq/l)	FREE	0	0	0	0	0	0
		TOTAL	0	05	25	2	6	9
	pH		752	675	648	551	448	418
	PEPSIN (Mett U)	CONC	±	0	78	462	117	QNS
		ACT	±	0	0	+	+	QNS
	Cl (meq/l)		NOT DONE					

Fig 35

By arbitrarily selecting a decrease of 1 pH unit as evidence of acid secre *tion, in a group of 20 patients who showed no titratable free acid after the* test meal alone, we found only 9 who might be considered anacid when judged by this standard of pH change When the same group was retested with histamine, 15 were still classified as failing to respond to histamine because of *no titratable free acid but only 5* failed to show a pH change in the gastric contents of one or more pH units

The first part of the question which is even more fundamental is really more difficult to answer Dr Hollander has found the pH of gastric mucus following eugenol stimulation to range between pH *7 9* and *8 6 In* our studies, using sodium dodecyl sulfate as the stimulant, the pH of the mucus obtained ranged between 7 5 and 8 7 It is apparent therefore, that with an average pH for mucus around 8 2, titration for total acidity in gastric contents

must be carried to such a pH, since some mucus would be present in all gastric samples which would combine with some of the free hydrochloric acid

Titration for total acidity, therefore, cannot be considered complete unless carried to the pH of mucus Under the circumstances it becomes apparent, then that gastric secretion cannot be considered entirely devoid of parietal cell secretion, unless the gastric secretion is at all times at a pH approximately 8 2 or higher If such conditions are imposed the occurrence of a complete gastric anacidity must be very rare indeed and it is probable that most cases so classified are examples of a very low rate of acid secretion with neutraliza tion—actually examples of clinical "hypoacidity

We feel that we should not attempt a final answer to the questions which we have posed until the problem has been given further study But we believe that our present evidence indicates clearly that the clinical interpretation of gastric anacidity needs reconsideration

QUESTIONS AND ANSWERS

DR BOCKUS Would you like to express your opinion on the effect of com plete vagotomy or vagectomy on the total output of gastric mucin?

DR HOLLANDER We have had no experience whatever in relation to the effect of vagotomy on mucus secretion The problem is an important one but we do not yet have available for such purposes a satisfactory and easily appli cable method for determining the amount of mucus in a gastric sample Some methods are described in the literature and we are at present engaged in comparing a number of these with a view to determining which is most reliable for our various experimental and clinical objectives

We have wondered whether there is any good evidence for believing that mucus secretion is under parasympathetic control in the stomach There are some reports in the literature to the effect that when the vagi are cut and the peripheral ends are stimulated electrically, there is an increase in mucus secretion, also that when a vagomimetic agent like mecholyl is injected an increase in mucus output occurs But you must remember that under both these circumstances there is also an increase in motor activity of the stomach, or of the pouch as the case may be, and as a result of that motor activity alone it is conceivable that there would be some mechanical expression of mucus The only attempt we have made at investigating this particular question is a study done some years ago on the influence of pilocarpine injections on vagotomized (Heidenhain) pouches When the experiments were done with the animal in a supporting stand such as is generally used for these purposes and with a rubber catheter inserted into the pouch as part of the collecting device we found that not only was there an increase in acid and in pepsin output after injection of the drug but also an appreciable increase in the visible, insoluble mucus

We then repeated the experiments with the same dosage of pilocarpine, using the same animals under essentially the same experimental conditions except for one—which modified condition was made possible by the fact that the pouch had been originally prepared with a sphincter at its mouth, so that the secretion which was formed during the experiment could be retained inside the pouch for as long as necessary Hence, in the second set of experiments, instead of keeping the animal upright in the collecting stand as usual, we left the animal in its cage with dressing on, thus retaining the secretion in the pouch instead of draining it off continuously by an indwelling catheter Thus the secretion was now formed in the absence of the collecting device, and therefore without any solid object in contact with the mucosa Consequently, in the first type of experiment, any motor activity of the pouch would result in rubbing of pouch mucosa against catheter, thereby inducing mechanical stimulation of mucus secretion, whereas in the second set of experiments, such mechanical stimulation will be absent We found the following results

In the first set of experiments, with the catheter in place, there was a significant output of mucus following pilocarpine injection, but in the second set of experiments, without the catheter in situ during secretion, the amount of mucus was reduced by about 50 per cent on the average This holds for insoluble, visible mucus only, for we did not determine the soluble variety Furthermore, there was a significant rise in acidity (on the average) in the second set of experiments as compared with the first, and this observation jibes with the observations on mucin content—i e, there appeared to be a greater neutralizing power when more insoluble mucin was present We concluded therefore, that at least part (and possibly even all) of the mucus which had been reported in the past as being evoked by parasympathetic stimulation came not by direct neural stimulation of the glands, but indirectly by vagal stimulation of the musculature You must remember, also that as yet there is no histologic evidence for the existence of postganglionic secretory fibers from Meissner s or Auerbach s plexus to the surface epithelium of the stomach Although such evidence has been reported repeatedly for the parietal cells and the peptic cells, there is none for the mucus cells Consequently, I consider that it is, at present, open to serious question whether there is any such neural innervation of the mucus glands whatever, and, therefore, whether vagectomy will seriously interfere with mucus secretion

Dr Bockus Thank you, Dr Hollander I have had the opportunity of observing a patient who was subjected to a complete vagotomy and whose insulin test remained negative for a period of a year I had occasion to attempt to remove his fasting gastric residuum several mornings when he had been allowed to go without his urecholine the previous day I was impressed with the presence of a large mucinous mass which was recovered from the stomach under these circumstances It was for this reason that I wondered whether the secretion of mucin might be greater in the absence of vagus innervation when there is the traumatic effect which you have brought out? Have you noticed this tendency in any of your vagectomized patients in New York?

Dr Hollander. Yes, but this increase in retained mucus may have resulted

from topical stimulation (mechanical or chemical) of the mucosa, because of the increased gastric retention following vagectomy Or perhaps it was chiefly salivary in origin, rather than gastric

Question How reliable is the present way of determining acidity in the fractional test meal and can one draw conclusions about the efficacy of substances supposedly antacid in their effect?

DR SHAY Present clinical methods for titrating gastric acidity in patients who have free hydrochloric acid in their gastric secretion are quite adequate It is certainly not going to alter one s clinical opinion if the acidity of a gastric sample is 25 instead of 20 milliequivalents (clinical units)

In the patient with gastric anacidity, however I am convinced that titration methods alone are inadequate especially since the clinician often places so much emphasis on whether or not the stomach fails to secrete acid after histamine

As a measure of the efficacy of antacids I would not consider titration for free acid alone as adequate if the antacids are being studied in relation to the ulcer problem It would probably take us too far afield to discuss the relative importance of acid and pepsin in the ulcer problem My own opinion would lay stress on the pepsin—its importance rests on its activity and to be active the pH of the medium plays its part As pointed out in the early portion of my discussion the proteolytic end point, the pH at which peptic digestion stops completely is pH 5 0 Since by titration for free acid one can only say that the pH of the gastric contents is above 3 5, when no titratable free acid is found such a method could not really tell one whether the antacid that is being studied brought about sufficient neutralization to completely inhibit peptic digestion

DR BOCKUS Then in your opinion, Dr Shay the stomach must be totally dead before it ceases responding to histamine I suspect that based upon your findings so demonstrated here this morning real achylia gastrica must be exceedingly rare in the live patient

DR SHAY I suspect, Dr Bockus that your statement is nearly correct

Question Has dibutoline any clinical advantage over the use of atropine or its derivatives?

DR LORBER Clinical reports on the use of dibutoline as an antispasmodic indicate that the drug may be effective when atropine fails to give relief Dibutoline in the doses used, has not been noted to produce the unpleasant excitation of the central nervous system which often occurs after the admin istration of atropine The xerostomia produced by both drugs is less trouble- some when dibutoline is administered

Gastric Neoplasms

COMMENTS ON THE ROENTGEN DIAGNOSIS OF GASTRIC TUMORS

ARTHUR FINKELSTEIN, M D

It would be presumptuous to present a systematic review of the ordinary roentgen diagnostic features of gastric tumors to a group of this type Perhaps it will be more interesting to review certain problems with which we have been confronted For the purpose of informal discussion these difficulties may be grouped as problems arising because of (1) the location of the lesion (cardia and prepyloric region or antrum), (2) small size (3) configuration (benign vs malignant), (4) non-opaque residue, (5) technic

PROBLEMS DUE TO LOCATION

In the *cardia* difficulty arises not merely in distinguishing a benign from a malignant lesion A major problem is the recognition that any lesion at all is present Every radiologist of experience has met the distressing circumstance of completely failing to recognize a carcinoma sometimes a very sizable one, of the cardia

Case 1 This was a man aged twenty four, with a recent history of dysphagia In the exposure made in the erect position (Fig 36*A*), one sees faintly outlined by a slight coating of barium a somewhat polypoid small mass in the medial aspect of the cardia near the esophageal orifice In the recumbent position (Fig 36*B*) the entire gastric lesion is obscured by barium in practically every projection (which emphasizes the importance of the erect exposure, particularly the outlining of the cardia by air when a lesion is suspected in that area) A small quantity of barium seen in the lower esophagus (Figs 36*A* and *B*) suggests that the esophagus is normal However, when barium is present in sufficient quantity to really distend the lower esophagus it is evident that an irregularly constricting lesion is present as demonstrated both in the recumbent (Fig 36*C*) and erect (Fig 36*D*) positions At operation this young man was found to have a carcinoma of the cardiac end of the stomach invading the lower esophagus

When a mass is found or suspected in the cardiac end of the stomach a very careful film study of the adjacent lower esophagus is required since non obstructing neoplasms of the esophagus are very readily overlooked fluoroscopically Conversely the importance of a careful examination of the upper stomach is indicated in every instance of any lesion of the lower esophagus which could by any stretch of the imagination be a neoplasm, no matter how atypical

Case 2 The film of this patient s chest while erect includes the upper abdomen, a small section of which is reproduced here (Fig 37) The cardiac end of the stomach is distended by swallowed air which outlines a small smoothly rounded soft tissue density situated medially This proven carcinoma of the cardia *is visualized better in this exposure* than in any films made subsequently after administration of a barium meal

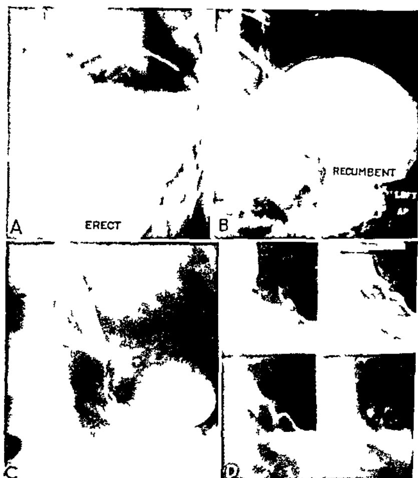


Fig 36 A man aged twenty four with carcinoma of the cardia partially outlined in air bubble A but obliterated by excess barium B Invasion of lower esophagus is demonstrated only when a large bolus of barium is passing through C and D

In our experience, this situation has not been encountered frequently, but when it is observed it has been a great diagnostic aid So much so, that when difficulty arises in identifying or excluding a cardiac lesion, we have frequently introduced air by administering an effervescent mixture, or preferably by passing a gastric tube and inflating the cardia by means of a manometer under fluoroscopic control The addition of a small amount of barium to provide double contrast has also been helpful at times

Case 3. Polypoid lesions of the upper portion of the body near the cardia are likely to be overlooked unless they are sizable, because the high position at the costal margin may prevent adequate compression studies; when the mucosal pattern is not well visualized, such tumors may be readily overlooked. In the present case, the exposure made in the erect position (Fig. 38*A*) discloses no obvious abnormality, although there is a suggestion of slight encroachment on the lumen of the body. A spot compression exposure of this area suggests a polypoid lesion, but it was not constantly demonstrable in other films. However, the appearance was regarded as suspicious and reexamination was recommended in an effort to obtain more conclusive spot compression exposures and possibly double contrast by inflating the barium coated stomach with air.



Fig. 37. Carcinoma of cardia seen best when outlined by air in erect film of chest.

Through some misunderstanding, the patient did not return until three months later. At this time a very extensive carcinoma of the upper part of the stomach was readily visualized when excess barium was pushed distally by the compression paddle (Fig. 38*C*). On the same occasion, this enormous mass could be easily obscured when much barium was present (Fig. 38*D*), emphasizing the treacherous nature of lesions at this site.

The *antrum*, and especially the *prepyloric* segment, are locations which are particularly prone to present baffling diagnostic problems. In this area, unlike the cardia, there is usually no difficulty in recognizing that a pathologic condition is present. But our recent experience has brought forth a succession of two types of deformities which have presented configurations which might be benign or malignant. The first to be considered will be the rather smoothly

constricting prepyloric lesion, continuous with the pylorus, the second will be the atypical ulcerating lesions of the antrum

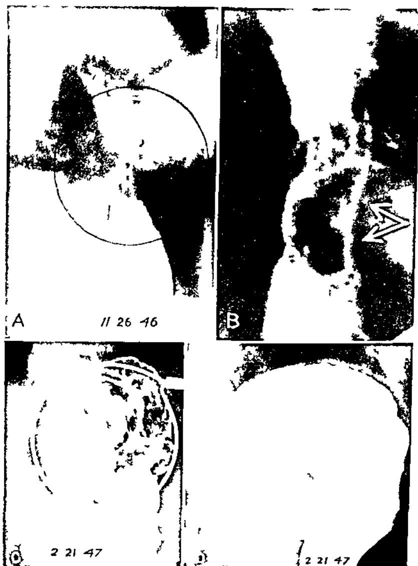


Fig 38 Suspected early malignant invasion of upper portion of body of stomach A visualized best in spot compression exposure B On delayed reexamination three months later an enormous carcinoma is shown by compression C, but is completely obscured by excess barium D

Case 4 This patient presents a smooth tubular narrowing of the prepyloric region (Fig 39*A*), which is seen better in close up in Fig 39*B* From the roentgen standpoint I know of no method for determining whether such a configuration is due to a benign or a malignant condition At operation benign hypertrophy of the prepyloric muscle was found We seem to be encountering

this condition with increasing frequency It comprises such an important diagnostic problem that it will be discussed in detail later in the program One might question whether such muscle thickening is due to disease elsewhere in the stomach Such speculation is not idle since in the present case a rather inconspicuous carcinoma of the cardioesophageal area was almost com-

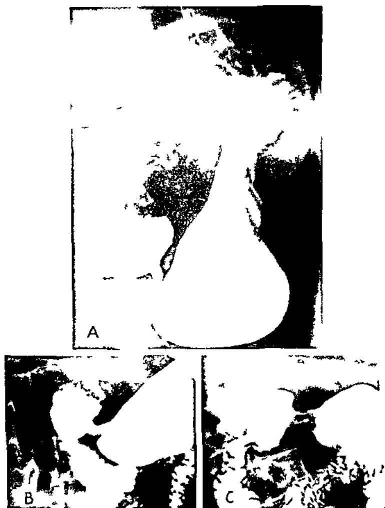


Fig 39 Tubular smooth narrowing of prepyloric area due to muscle hypertrophy but indistinguishable with certainty from a benign or malignant neoplasm

pletely overlooked because of the fluoroscopist s preoccupation with the obvious prepyloric disease The cardioesophageal lesion is not definitely identified in the present illustrations but presented a configuration similar to Fig 36

Case 5 This illustration of a typical ulcerating antral malignancy (Fig 40)

with its irregular constriction, polypoid mucosal pattern, and greater curvature ulceration, is presented for comparison with the following case

Case 6 This patient presents, along the greater curvature of the antrum, a smooth concave filling defect at the apex of which there is a small projection of barium indicating an ulcer crater (Fig 41) The configuration is constant and is not significantly altered by peristalsis, as the multiple exposures indicate The configuration suggests a small tumor with central ulceration My

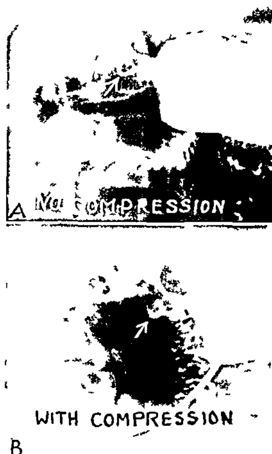


Fig 40 A rather typical antral carcinoma presenting a greater curvature ulceration Compare with Fig 41

interpretation was *that this was probably a malignancy with secondary ulceration* At operation only a benign ulcer was found If the x-ray examination had provided a satisfactory mucosal pattern visualization without evidence of nodular infiltration and if sufficient attention had been paid to the smooth narrow incisura on the curvature of the stomach opposite to the ulcer crater, perhaps *the correct* x ray diagnosis would have been made The patient s symptoms, and the radiologic interpretation of probable malignancy, made it

seem unwise to delay operation in order to await the response of the lesion to a medical regimen with subsequent x ray examination

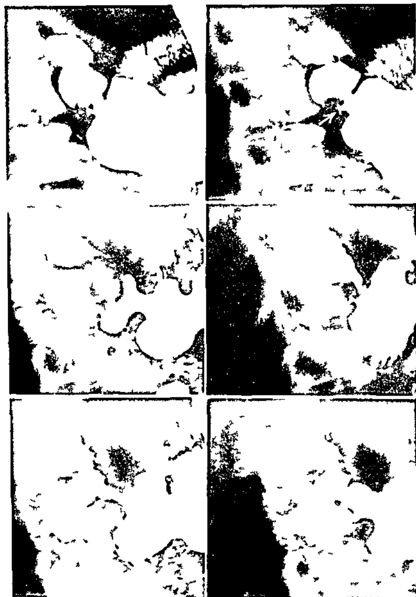


Fig 41 An uncommon benign ulcer of the greater curvature of the antrum simulating an ulcerating tumor Note incisura on opposite curvature Compare with Fig 40

Case 7 This fifty four year old man gave a long history of tuberculosis during which one kidney and one testis became involved and were surgically

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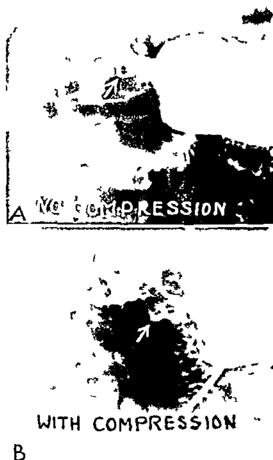


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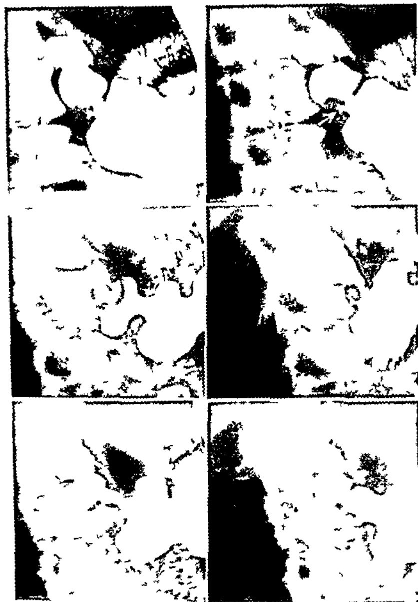


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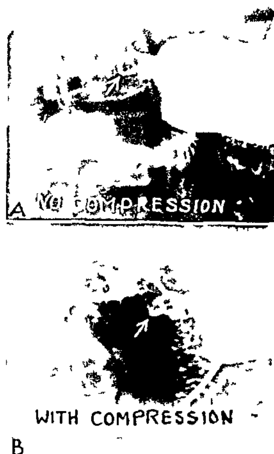


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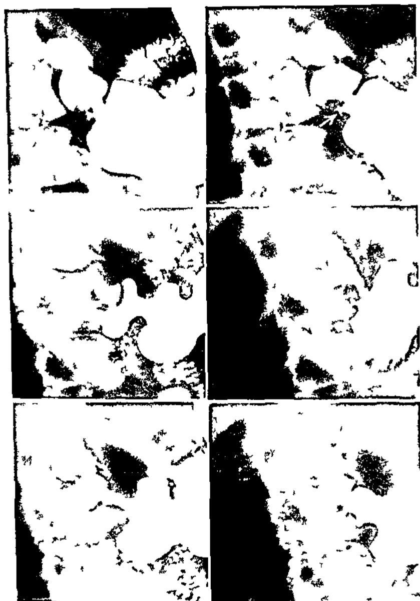


Fig 41 An uncommon benign ulcer of the greater curvature of the antrum simulating an ulcerating tumor Note incisura on opposite curvature Compare with Fig 40

Case 7 This fifty four year old man gave a long history of tuberculosis during which one kidney and one testis became involved and were surgically

removed He had rather extensive pulmonary tuberculosis at the time of our first x-ray examination of his stomach His gastric acidity was low The examination after a barium meal reveals a type of ulcerating antral lesion which is encountered more frequently than the preceding cases In Fig 42*A* a large collection of barium is identified in a large ulcer crater surrounded by a radiolucent 'halo in which a somewhat polypoid mucosal distortion and destruction are seen When the patient is slightly rotated and slight compression is made upon the stomach, the lesion is seen to comprise a filling defect along the greater curvature associated with an ulceration In no position is it possible to demonstrate the ulcer crater projecting outward as a niche—an

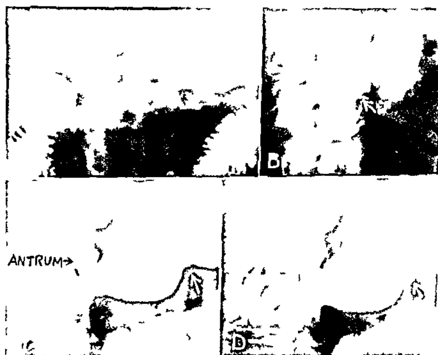


Fig 42 An ulcerating antral malignancy demonstrated best by compression A The crater does not project in profile because it is surrounded by a mass B The lesion is almost completely obscured by excess barium in C and D (arrows) Prepyloric narrowing proved due to muscle hypertrophy

important diagnostic point since it suggests that a tumor is projecting into the gastric lumen, with secondary ulceration of this mass When compression is not applied, the lesion is almost entirely obscured except for a smooth indentation along the greater curvature suggesting a peristaltic wave except for its constancy (*Fig 42C and D*)

The long history of extensive tuberculosis, and the persistent rather smooth prepyloric narrowing suggesting old inflammatory involvement, made a diagnosis of gastric tuberculosis very enticing Resisting this temptation with some difficulty, a roentgen diagnosis of an ulcerating malignancy was given first choice, tuberculosis a less likely possibility At operation an ulcerating

malignancy was found, corresponding to the radiographic appearance The prepyloric narrowing was due to benign thickening of the antral muscle

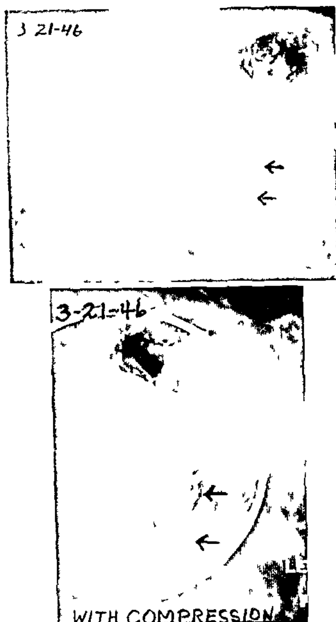


Fig 43 Small benign polyps of stomach shown best by compression They were completely obscured when stomach was filled with barium (not illustrated)

PROBLEMS DUE TO SMALLNESS OF TUMOR

The diagnosis of malignancy of the stomach in its early stage implies the detection of very small tumors or infiltrations, by methods now available This

requires complete visualization of the gastric mucosal pattern It is probable that many cases of early carcinoma of the stomach present a configuration similar to that shown in Case 8, Fig 43 When much barium was present, these filling defects were completely obscured At operation they were found to be benign polyps It is problematical that such small lesions would be frequently detected by methods of mass x-ray survey now being used

Case 9 Small pedunculated polyps present a special problem in diagnosis since their ability to shift position may prevent their detection Fortunately, they are uncommon The present case is that of a verified pedunculated polyp arising in the prepyloric region, but at times prolapsing into the duodenal cap Adequate visualization of the mucosal pattern of the cap and antrum is re-

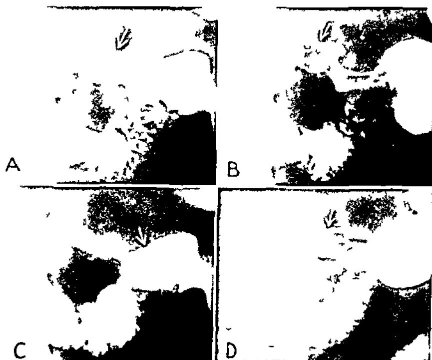


Fig 44 A pedunculated polyp which has prolapsed into the duodenal cap A and B but slips back into the prepyloric area C and D from which the pedicle arises

quired to demonstrate this behavior Figure 44*A* shows the polypoid tumor presenting a somewhat cloverleaf filling defect in the base of the cap In Fig 44*B* the pedicle is inferred because of obliteration of the mucosal pattern of the pylorus, the normal mucosal pattern of the antrum excludes a second tumor there In Fig 44*C* the cap presents a normal mucosal pattern and the polyp can be faintly seen in the antrum When the antrum is not distended by barium the polyp is clearly visualized in it (Fig 44*D*)

PROBLEMS OF CONFIGURATION BENIGN VS MALIGNANT

The most common problem in the x-ray diagnosis of gastric lesions is not the detection of the lesion but in the differentiation between benignancy and

malignancy Although in most instances the configuration of the diseased segment of the stomach permits a ready differentiation a smaller but very important group of benign and malignant conditions tend to mimic each other For the purpose of the present discussion these may be grouped according to their most prominent roentgen appearance as ulcerating lesions smooth stenosis, especially in the pyloric area small ridge like elevations simulating large rugal folds, infiltration producing chiefly a stiffened gastric wall, and certain rare lesions

A large proportion of *ulcerating lesions* follow the dictum that those arising from the lesser curvature are usually benign, and those arising from the greater curvature are usually malignant This provides a useful attitude for the preliminary evaluation of such a gastric deformity But not all ulcerations

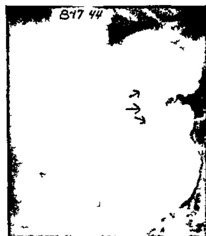


Fig 45



Fig 46

Fig 45 A large lesser curvature benign ulcer with surrounding inflammatory swelling and an incisura of the opposite curvature was mistaken elsewhere for an extensive malignancy

Fig 46 On reexamination after three weeks of medical treatment marked improve ment is obvious

arise precisely from the lesser or greater curvature Furthermore the roentgen appearance of each lesion must be studied in detail since criteria other than location may be the deciding factors Specifically, aid may be obtained if one can recognize nodularity in the mucosal pattern or considerable asymmetry and irregularity in the soft tissue swelling surrounding the ulcer crater if it is in a malignancy Or one may place considerable reliance on the appearance of mucosal folds smoothly radiating from the ulcer crater especially if a constant incisura is encountered on the opposite gastric wall in a benign ulcer But unfortunately these criteria are not infallible

Case 10 Figure 45 shows the appearance of the stomach as recorded by another radiologist who made a diagnosis of extensive malignancy of the upper part of the body of the stomach and gave the patient s family a hopeless

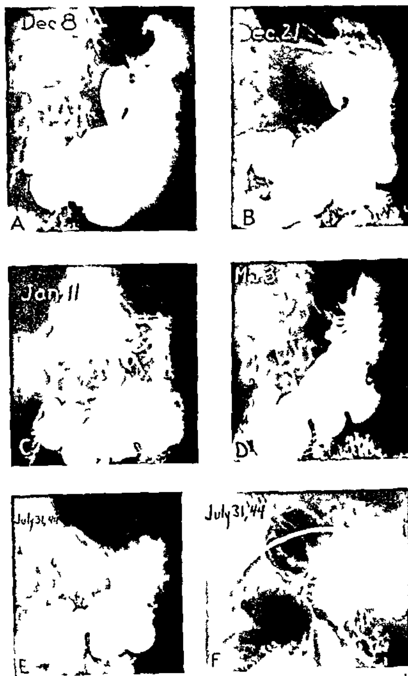


Fig 47 Typical large benign lesser curvature ulcer with large accessory pocket due to local perforation A The usual stages of healing are shown in B to F Compare with Fig 48

prognosis Dr Thomas Johnson, who was attending the patient, regarded this diagnosis somewhat skeptically because the deformity could be analyzed as being composed of a benign lesser curvature ulcer with the usual surrounding

inflammatory swelling plus a prominent incisura of the opposite greater curvature The patient was placed on a medical regimen and when we had the opportunity to examine her three weeks later (Fig 46) a striking decrease in size of the ulcer crater had occurred The deformity of the opposite curva-

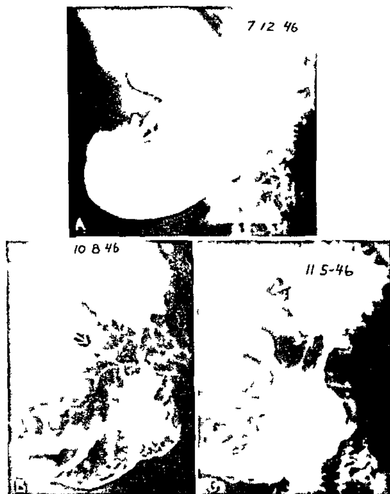


Fig 48 Localized perforation and accessory pocket formation A showing satis factory regression within three months B Recurrence of local perforation one month later C Roentgen interpretation benign ulcer with local perforation At operation the surgeon made the same diagnosis of the gross specimen Pathologist s report adenocarcinoma with local perforation Compare with Fig 47

ture was obviously an organic incisura of inflammatory etiology (compression studies not reproduced here revealed smoothly radiating mucosal folds similar to Fig 47*F*)

Case 11 Benign ulcers of the stomach even when of large size, usually follow a typical pattern of change on follow up x ray examinations when the

patient is placed on an adequate medical regimen If one reexamines such patients intermittently during a period of several months, the sequence of changes is often that illustrated in Figs 47*A* to *F*, even when local perforation has produced a large accessory pocket as in the present case

The large accessory pocket dominates the picture in our first examination of December 8, 1943 (Fig 47*A*) Three weeks later the pocket was consider ably smaller, as shown in Fig 47*B* By January 11, 1944, the pocket had almost completely disappeared as seen in Fig 47*C* On March 3 a small ulcer crater persists along the lesser curvature and an organic incisura is appearing



Fig 49 Malignant lesser curvature ulceration presenting certain roentgen features simulating benignancy

along the lesser curvature at a more distal level as is usually the case By July 31, 1944, the ulcer crater was almost completely healed, as indicated in Fig 47*E* But the compression exposure (Fig 47*F*) made on the same date indicates the extent of residual scarring producing radiating mucosal folds, a stiffened wall at the site of a small residual niche, and an organic (fibrotic) incisura on the opposite greater curvature After one has encountered a number of such cases, one is apt to adopt an attitude of jaunty self assurance of one's diagnostic acumen But not for long!

Case 12 At the time of our first x ray examination on July 12 1946, this patient presented the configuration of a large localized perforation with an

accessory pocket extending somewhat anteriorly from the lesser curvature Broad mucosal folds are noted radiating from the site of perforation (Fig 48*A*) Our interpretation was that the lesion was probably a benign ulcer with local perforation We felt that this diagnosis was confirmed when repeated x ray studies showed progressive improvement so that by October 8, 1946, the lesion had almost completely disappeared (Fig 48*B*) One month later symptoms recurred and the roentgen study (Fig 48*C*) revealed a configuration of a recurrent local perforation similar to that in Fig 48*A* Again my interpretation was that the lesion was benign The patient was promptly operated upon

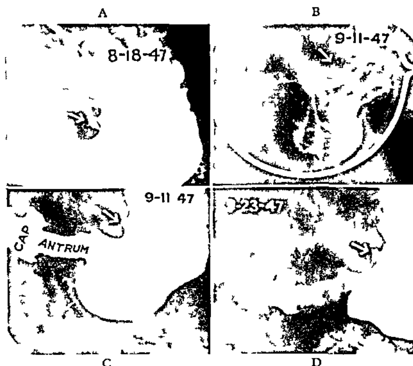


Fig 50 A typical benign lesser curvature ulcer A partially healed within three weeks B and C Exacerbation two weeks later Tubular antral narrowing proved on operation to be combination of scarring from old ulcer plus muscle hypertrophy

because of the failure of medical treatment and when the surgeon examined the excised specimen he did not recognize any evidence of malignancy Subsequent histologic examination proved the lesion to be a carcinoma It is therefore evident that the extensive inflammatory changes probably incident to the localized perforation obscured the relatively inconspicuous carcinoma Although the features of this case are unusual they emphasize that so called typical roentgen signs or at least the radiologist s interpretation of them are not infallible

Ulcerating malignancies along the lesser curvature do not usually mimic

benign lesions so closely Case 13, Fig 49*A*, presents a rather shallow, broad ulceration arising from the lesser curvature proximal to the incisura angularis Although a compression exposure demonstrates rather orderly radiation of mucosal folds (*Fig* 49*C*), close inspection indicates a peculiar nodularity immediately adjacent to the ulcer as seen in Fig 49*B* A roentgen diagnosis of malignancy was made because of this nodularity, because of the shallowness and breadth of the ulceration, and to a slight extent because of the absence of an incisura although the latter was not an important factor This diagnosis was verified at operation

The diagnostic problem of *stenosis of the antrum* was alluded to earlier (Figs 39*B* and 42*C*) Case 14 demonstrates the successive stages in the observation of a benign lesser curvature ulcer from the time of first examination on August 18, 1947 (Fig 50*A*), regression on reexamination three weeks later (Fig 50*B* and *C*) followed by exacerbation on September 23 (Fig 50*D*) Throughout this period the peculiar tubular antral narrowing remained unchanged Although a malignant infiltration could not be excluded as the explanation for the latter appearance, it seemed more likely that it was the result of previous inflammation At operation the scar of a previous antral ulcer was found associated with an antral gastritis and fibrosis of the walls of the antrum

Case 15 This woman in her early seventies is a patient of Dr Monaghan Her x ray examinations were made by Dr R Bromer at the Bryn Mawr Hospital Figure 51 reveals a constant, irregular antral constriction associated with considerable mucosal distortion A differentiation between an inflammatory and a malignant involvement could not be made On gastroscopy Dr Monaghan found the mucosa of the entire stomach involved in a peculiar infiltrative process which might be either inflammatory or neoplastic, no distinct antral lesion was identified Since the patient s cardiovascular status was very poor, and since definitive treatment would have required total gastrectomy in view of the gastroscopic findings surgery was deemed inadvisable X-ray examination seven months later (Fig 52) showed no significant improvement Reexamination after an interval of six months (Fig 53) demonstrates definite reexpansion of the antrum in which some distortion of the mucosal pattern is seen, it was then evident that the disease was a severe antral gastritis, as was also indicated by repeated gastroscopic examinations The final study (Fig 54) was made five years after the first observation and demonstrates a fairly normal antrum In retrospect it would seem quite possible that the deformity noted in the earlier studies may have been due to ulcerations not recognized radiologically or gastroscopically

At present we have found no reliable method for differentiating inflammatory from neoplastic (benign or malignant) prepyloric lesions or muscular hypertrophy on the basis of a single x-ray examination The problem is so acute and frequent that it will be discussed in detail later in this program

Small *ridge-like tumors* may simulate the configuration of a large or giant rugal fold and offer the gastroscopist as well as the radiologist great difficulty in differentiation Case 16 is also Dr Monaghan s patient who was x rayed

Fig 51



Fig 52





Fig 53



Fig 54

Figs 51–54 Irregular prepyloric stenosis simulating carcinoma but due to severe gastritis Progressive improvement over a period of five years

by Dr R Bromer at Bryn Mawr Hospital The first roentgen study made on October 1, 1940 demonstrated a peculiar broad radiolucent ridge seen best at the margin of one exposure (Fig 55*A*) which includes only the antrum and

duodenum It was uncertain whether the condition was due to malignant infiltration or whether it was a benign giant rugal fold The patient was placed on a medical regimen, and reexamination eighteen days later (Figs 55*B* and *C*) showed only slight improvement Because neoplasm could not be definitely excluded, further temporizing was considered unjustified The stomach was promptly resected and a diagnosis of benign giant rugal folds was established

Case 17 This patient is presented through the courtesy of Dr J W Hundley The examination of the stomach made elsewhere (Fig 56) discloses slightly nodular broadening of the rugal folds of the upper portion of the body of the stomach, these are of course seen only when a mere mucosal coating of barium is present and are completely obscured when the stomach

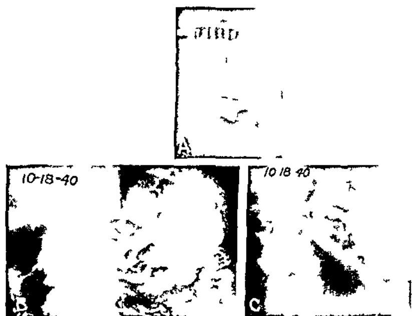


Fig 55 Giant rugal folds simulating malignancy

is filled with barium Multiple exposures showed a fixity of contour of these ridges, and no evidence of peristalsis is observed From the roentgen stand point this appearance might be produced by various conditions, especially submucosal carcinoma, lymphoblastoma, leukemic infiltration or benign giant rugal folds In the present case, on resection the patient was found to have Hodgkin s disease of the stomach with submucosal infiltration accounting for the ridge-like prominence of the rugal folds

Infiltrative lesions producing chiefly a stiffening of the gastric wall may be associated with demonstrable changes in the rugal pattern Such abnormalities of the rugal pattern whether effaced, accentuated, or distorted, may help the radiologist to guess at correct etiology but do not offer reliable diagnostic data







Fig 56 Broadened slightly nodular folds due to infiltration by Hodgkin s disease



Fig 57

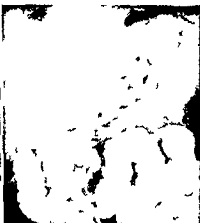


Fig 58

Figs 57 and 58 Tubular narrowing of stomach with nodular mucosal pattern due to linitis plastica type of diffuse carcinoma

Case 18 Diffuse infiltration may produce tubular narrowing of the stomach as in Fig 57, and if the mucosal pattern is well visualized and is quite prominently nodular as in Fig 58, there is strong likelihood that it is due to a diffuse infiltrative carcinoma of the linitis plastica type At operation such malignant infiltration was found Syphilis of the stomach could have produced a very similar picture

Case 19 A diffuse nodularity throughout the body of the stomach without stenosis (Fig 59) (the apparent antral narrowing is due to a peristaltic wave) led to a roentgen interpretation of diffuse polyposis At operation the entire body of the stomach was infiltrated by a linitis plastica type of carcinoma, no polyps were found



Fig 59 Diffuse infiltration by carcinoma throughout body of stomach with polypoid mucosal pattern but without stenosis

Case 20 This case is being presented for comparison with the preceding patient The present patient, a male Negro aged thirty years, was under Dr Monaghan s care The x-ray examination of the stomach made by Dr R. Bromer at Bryn Mawr Hospital (Fig 60) demonstrates a slightly irregular antral narrowing and slight nodularity of the mucosa of the upper portion of the body somewhat similar to Fig 59 The patient was known to have a strongly positive Wassermann reaction A definite differentiation between syphilis and carcinoma of the stomach could not be made radiologically or gastroscopically The patient was given intensive antiluetic therapy by some other physician without Dr Monaghan s knowledge A Herxheimer reaction

occurred precipitating complete gastric obstruction for which a laparotomy was performed The surgeon, who was aware of the possibility of lues, found the lower portion of the stomach involved in a doughy mass which did not feel malignant Tissue was removed for biopsy and no other surgical measures were taken The histologic findings were consistent with syphilis The patient made a good clinical recovery The gastric deformity demonstrable by x ray improved very slowly, but ultimately disappeared Dr Monaghan and I have seen other cases in which gastric syphilis could not be distinguished from carcinoma gastroscopically or radiologically



Fig 60 Irregular antral narrowing due to syphilis simulating localized malignant infiltration

Case 21 Localized infiltration of the wall of the stomach by an inflammatory process may result in a stiffened appearance which when associated with local distortion of the rugal pattern, cannot be distinguished radiologically from malignant infiltration (Fig 61) Sometimes the differentiation may be made by gastroscopy which in the present case disclosed a rather severe degree of gastritis and no evidence of malignancy The patient has remained relatively symptom free for over five years since that time so that the gastro scopic diagnosis seems verified

Case 22 This seventy year old woman stated that she had undergone a gastric resection some twenty years ago in France Recently she had developed somewhat obscure upper abdominal pain chiefly on the left Extensive studies made elsewhere failed to demonstrate the cause of her symptoms Our

first x-ray examination (Fig 62) disclosed a subtotal gastric resection and a well functioning gastrojejunostomy A surprising feature of this study is the

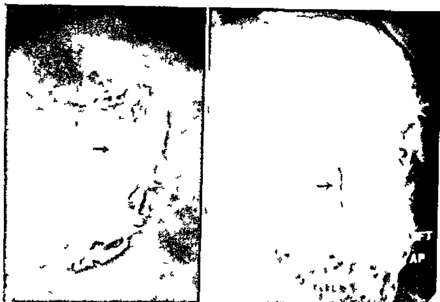


Fig 61 Stiffened area of lesser curvature of the body of the stomach associated with mucosal distortion due to hypertrophic gastritis Simulates localized malignant infiltration



Fig 62 Polypoid filling defect in stomach adjacent to site of resection and jejunostomy suggests a tumor Proved due to peculiar infolding of gastric wall by previous surgery

peculiar smoothly irregular radiolucency situated on the gastric side of the stoma, presenting a polypoid configuration This filling defect was present constantly, and changed very slightly in size and configuration in the various

exposures My interpretation of this radiolucency was that it probably represented some peculiar type of tumor, possibly benign On gastroscopic examination a portion of an atypical smooth soft tissue elevation was seen but a definite diagnosis was not made At operation the surgeon found that the puzzling radiolucency was produced by a certain type of infolding of the gastric walls at the site of the original resection—a surgical defect which he facetiously christened ' French pucker

Such a configuration does not result from surgical technics now employed in this country But this unusual appearance serves to remind us that less conspicuous surgically produced deformities are commonly encountered following operations on various portions of the gastrointestinal tract Particularly when the stomach has been resected because of carcinoma it is important to make an x ray examination within a few weeks to serve as a base line for future reference if a recurrence is subsequently suspected

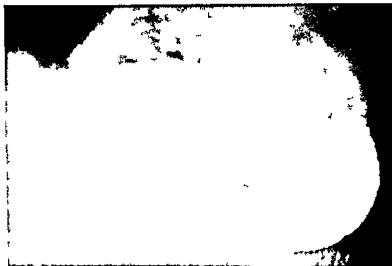


Fig 63 A large gastric mass with a somewhat central crater Leiomyosarcoma

Certain *rare tumors* involving the stomach present special problems, with reference either to benignancy versus malignancy (Case 23) or to primary location within or outside the stomach (Case 24)

Case 23 This is Dr Monaghan s patient x rayed elsewhere A large smoothly outlined mass occupies the upper third of the body of the stomach (Fig 63) The marginal outlines are sharply defined and there is no nodularity of the adjacent mucosa such as might suggest surrounding infiltration Near the upper margin of this globular soft tissue mass there is a small collection of barium indicating a deep ulceration or necrosis In brief, it is the picture of a localized globular mass presenting a small somewhat central crater This is a rather characteristic configuration of a gastric leiomyoma (although not all of these present craters) Unfortunately a leiomyosarcoma presents an identical configuration The differentiation between the benign and malignant forms

first x-ray examination (*Fig 62*) *disclosed a subtotal gastric resection* and a well functioning gastrojejunostomy A surprising feature of this study is the



Fig 61 Stiffened area of lesser curvature of the body of the stomach associated with mucosal distortion due to hypertrophic gastritis Simulates localized malignant infiltration



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peculiar smoothly irregular radiolucency situated on the gastric side of the stoma, presenting a polypoid configuration This filling defect was present constantly, and changed very slightly in size and configuration in the various

is routinely intubated prior to x ray examination whenever it is known that the patient has a non-opaque residue, or when such fluid is identified after the first swallow of barium In this connection too much emphasis cannot be

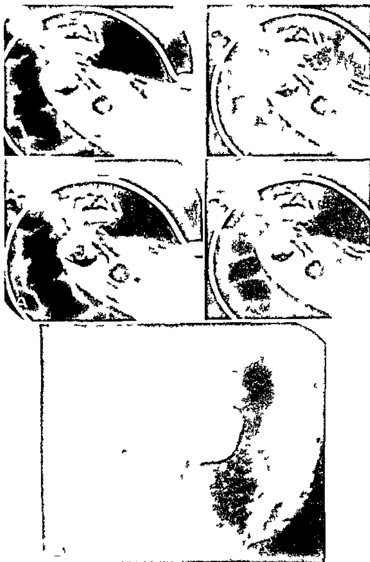


Fig 65 Multiple filling defects in antrum simulating polyps A but due to pieces of food Absent on reexamination after removal of non-opaque residue B

placed on the importance of completing the aspiration under fluoroscopic control, immediately before administration of the barium meal

Case 25 This patient had gastric retention secondary to a stenosis of the mid portion of the duodenal cap In our first examination (Fig 65*A*), at least

often cannot be made radiologically At operation this patient was found to have a leiomyosarcoma

Case 24 This is a boy aged fourteen years, presenting a large mass in his left upper abdomen The mucosal pattern of his stomach presents a normal configuration except for a few small areas where the folds seem to "fade out" (Fig 64*A*) In the lateral view (Fig 64*B*) it is obvious that the stomach is being pushed forward The problem concerns the recognition of the primary site of the tumor Is it a primary gastric neoplasm extending beyond the lumen of the stomach posteriorly? Or is its origin in the retroperitoneal structures, displacing the stomach and invading it? In view of the patient's youth and other clinical findings the latter seemed the more likely explanation At operation a large retroperitoneal lymphosarcoma was found, secondarily invading the stomach

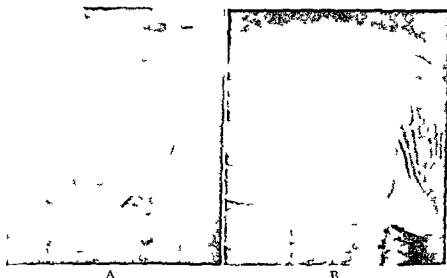


Fig 64 Displacement of the stomach and localized mucosal obliteration by a retroperitoneal lymphosarcoma infiltrating the gastric wall

Non-opaque residue in the stomach when the barium meal is given imposes a common diagnostic problem to which insufficient attention has been directed It is therefore being presented separately here, instead of discussing it under technic, where it would ordinarily be relegated It has long been recognized that lumps of food in the stomach may be mistaken for tumors It is not so widely appreciated that liquid residue, whether due to gastric hypersecretion, hypersalivation or ingested fluids, will commonly prevent recognition of a fairly sizable benign or malignant lesion Even when the lesion is not obscured, a small amount of non-opaque material will usually interfere with adequate visualization of the mucosa about the most prominent portion of the lesion and may thus prevent a decision regarding the true character of the disease process In our group, both the clinicians and the radiologists have become so impressed by the importance of this situation that the stomach

United States, and makes up approximately 25 per cent of all deaths due to cancer

In Great Britain and in Australia about 25 per cent of cancer deaths are due to carcinoma of the stomach, in Scandinavia, Holland Bavaria and Czechoslovakia more than one half of them, the highest proportion being Czechoslovakia s 66 per cent Gastric carcinoma is also one of the most common tumors among the Japanese accounting for 75 per cent of recorded cancer deaths in males, and 48 per cent in females It is also a common neoplasm in the Chinese, Cubans and Chileans

Various statistics obtained from Pack and Livingston, Walters, Gray and Priestley, Abrahamson and Hinton, Welch and Allen show a survival rate of 5 to 7 per cent once the diagnosis of gastric malignancy was made Despite the radical procedures being employed in gastric surgery today the survival rate remains low At the Mayo Clinic of a group of 10 890 cases, during the years 1907 to 1938 in which the diagnosis of gastric malignancy was established only 21.3 per cent of the group were resectable Of this group of patients who had resections performed and who survived the operation 28 9 per cent lived five years or longer, 20 4 per cent lived ten years or longer, 15 2 per cent lived fifteen years or longer 10 5 per cent lived twenty years or longer, and 6 3 per cent lived twenty five years or longer

Carcinoma of the stomach is usually moderately advanced before it produces any symptoms If a significant increase in the number of operable cases with hope for cure is to be attained, we must devise means of detecting the disease in its presymptomatic state

According to Bockus a very early diagnosis may occur in one of three ways (1) the accidental discovery of the lesion during periodic health examination, (2) its discovery at the time of a diagnostic check up for a previous benign lesion such as gastric or duodenal ulcer or (3) the finding of the cancer at the time of operation for some other condition

For the above reasons it is deemed necessary to provide a procedure for the detection of gastric malignancy in the stage when it will be amenable to treatment, and perhaps cure

Having had success in the diagnosis of preinvasive cancer of the cervix and uterus by studying the cytology of cervical secretions we decided to adapt this technic to a study of gastric sediment and washings

TECHNIC OF STUDY

For this study the patient reports to the Gastrointestinal Clinic at 8 30 A.M after having fasted for a period of twelve hours A 16 French Rehfuss tube is used in the extraction of gastric fluid To facilitate a more complete removal of the contents within the stomach additional perforations are made in the terminal 10 cm of the rubber tube When approximately 40 cm of the tube has been swallowed the patient is examined in the erect position under the fluoroscope The swallowing process is resumed and the metal tip of the Rehfuss tube is carefully observed In the ideal case the tip descends vertically and after reaching the greater curvature of the stomach the tube

four discrete rounded filling defects are noted in the antrum, maintaining a constant relationship and thus simulating a polypoid tumor These were due to food fragments as proven by reexamination after thorough gastric lavage and aspiration (Fig 65*B*)

TECHNIC

Problems of technic are largely obviated if the fluoroscopist is well trained He will then fluoroscope only when his eyes are properly dark-adapted, will examine the patient fluoroscopically in both the erect and recumbent positions, and will expose films in various projections with the patient in both the erect and recumbent positions No matter how skillful he claims to be, he will aim to record the mucosal pattern and the lesion on films in order to permit detailed study and future comparison In order to avoid blurring of outline by peristalsis or respiration, he will employ short exposures (preferably one-half second or faster) He will reexamine doubtful cases in a few days, or after an interval of several weeks, a longer interval is not justified when malignancy is in question

Nevertheless, when all precautions are taken, it must be admitted that at present there are very few instances in which the radiologic findings can be considered pathognomonic Even when one attempts strict adherence to diagnostic criteria which are generally considered reliable, there remain the problem cases such as we have just discussed Careful individualization of the x-ray examination in such instances will aid in their solution, particularly when close cooperation exists between the clinician and the radiologist, permitting ample discussion before evaluating dubious features

AN APPRAISAL OF THE CYTOLOGIC METHOD OF DIAGNOSIS AS APPLIED TO GASTRIC SEDIMENT

JOSEPH E IMBRIGLIA, M D , D SC , AND
MIECZYSLAW S LOPUSNIAK, M D , D SC

By far the most common and most important neoplasm of the stomach is carcinoma Twenty five to 35 per cent of malignant neoplasms which occur in the male, exclusive of lip and skin cancers, are gastric carcinomas In women it ranks second only to carcinoma of the uterus and breast No age group is exempt from the disease, although about 80 per cent occurs in persons after forty years of age We have noted a gastric carcinoma with metastases in a twenty four year old college athlete, and Anderson in his Textbook of Pathology states that he has seen carcinoma of the stomach in an eighteen year old boy

Carcinoma of the stomach causes almost 40,000 deaths every year in the

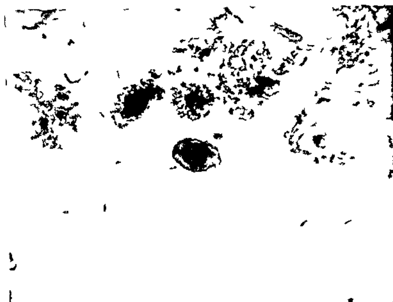


Fig 66 A single malignant cell from the case of intra epidermal carcinoma of the esophagus compare the malignant cell with the normal squamous cell

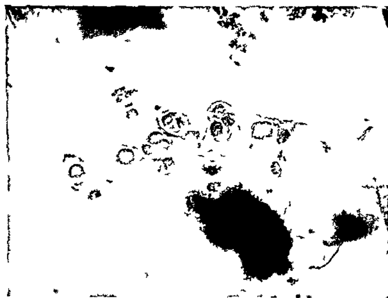


Fig 67 A group of malignant cells from the case of intra epidermal carcinoma of the esophagus note the variation in size of the nuclei

(2) an intra epidermal carcinoma of the lower one third of the esophagus
(3) a Hodgkin s disease of the stomach

slowly follows the contour of the greater curvature Massage of the tube along the costal margin from left to right may be required to advance the tube into the antrum If the distal end of the tube coils in the fundus of the stomach after the tip reaches the greater curvature of the body of the stomach, the tube should be withdrawn until the tip is at the cardiac orifice The fluoroscopic table is lowered to the horizontal position and the patient is turned onto his right side As the patient swallows, the terminal portion of the tube almost always enters the body of the stomach With the patient in the supine position, the progress of the tube is followed under fluoroscopic guidance until the tip enters the antrum of the stomach

Aspiration is carried on with the patient in the supine, right lateral and left lateral positions At times it may be necessary to tilt the fluoroscopic table in a semivertical position to completely empty the stomach

With the fasting specimen obtained, 200 cc of 1 per cent zinc chloride solution is slowly instilled in the stomach through the Rehfuss tube The solution is washed back and forth several times, the abdominal wall is massaged, the patient is rotated into various positions in an effort to bathe the entire mucosal surface of the stomach The fluid is then removed from the stomach

The fasting and lavage specimens are then centrifuged for twenty minutes at high speed Following centrifugation the supernatant fluid is drawn off and smears are made of the sediment on albumin coated slides, and fixed before drying in equal parts of 95 per cent ethyl alcohol and ether Following fixation the slides are now ready to stain by the method of Papanicolaou

RESULTS

In our group of 30 patients with gastric symptoms, 7 had carcinoma of the stomach, 1 an intra-epidermal carcinoma of the lower one-third of the esophagus (Figs 66 and 67), another had Hodgkin s disease of the stomach (Fig 68) Malignant cells were seen in the gastric sediment of all 9 cases

Eight of the above patients were explored one patient, a seventy-four year old colored female, died of congestive heart failure and an autopsy was performed Of the 8 patients explored, 5 had lesions which were resectable The autopsy of the seventy-four year old colored female showed a malignant polyp of the pylorus (Fig 69)

In 20 cases no evidence of malignancy was noted from cytologic study of the gastric sediment Four patients were explored Two were proved to have benign gastric ulcers, 1 had a surgical artefact due to a previous subtotal gastrectomy, 1 had no findings at surgery The gastric sediment was correctly diagnosed as negative in 20 instances

One positive cytologic report was rendered in a case later proved to have a benign gastric ulcer by operation

Of particular interest were the following cases all of which demonstrated malignant cells in a study of the gastric sediment

(1) a scirrhous carcinoma which involved only the distal one half of the stomach

We suggest this procedure as an adjunct to roentgenologic and endoscopic examinations in suspected lesions of the esophagus and stomach

At the conclusion of our study we sincerely hope that we can add a fourth and scientific method to the three methods previously quoted from Bockus for the early diagnosis of gastric malignancy

VALUE OF COMPLETE HEMATOLOGIC STUDY IN THE DIAGNOSIS AND PROGNOSIS OF ABDOMINAL MALIGNANCY

LAWRENCE H BEIZER, M D

Abdominal malignancy is a broad topic Lesions involving the gastrointestinal tract, the other visceral organs, and the lymphoid structures must be considered Together these may give rise to a variety of signs and symptoms Important among these are anorexia, weight loss, digestive disturbances, abdominal pain, jaundice, palpable masses, bleeding and any of the usual symptoms of anemia In view of this varied list one must consider in the differential diagnosis the various types of carcinoma of the gastrointestinal and genito urinary tract, and the malignant lymphomas and leukemias involving the visceral organs and lymphoid structures Multiple myeloma has to be considered because it may give rise to abdominal pain as well as anorexia and anemia The various idiopathic anemias have special features which require their consideration In pernicious anemia there is often anorexia and vague indigestion in sickle cell anemia, abdominal crises, in congenital hemolytic icterus there is jaundice and abdominal pain, and in aplastic anemia there is often anorexia and occasionally gastrointestinal bleeding The purpuras have to be considered, since in hemorrhagic purpura there is frequently gastro intestinal bleeding and in Henoch s purpura abdominal pain is an important feature It is important to realize that in abdominal malignancy the blood picture does not adhere to a single pattern This makes it necessary to have a complete hematologic examination in those instances in which the diagnosis is not clear Abdominal malignancy may reflect itself in the hematologic examination of the patient by the presence of an anemia, a leukocytosis a leukemoid reaction or an increase in the sedimentation rate The location and type of malignancy determine the type of hematologic reaction This is particularly well illustrated by the variety of types of anemia encountered By reviewing the underlying causes of anemia, it is apparent how this may occur

ANEMIA AND ABDOMINAL DISORDERS

Anemia may be due to acute blood loss, blood destruction, interference in blood formation, or deficiency of any of the necessary ingredients for blood



Fig 68 A cluster of malignant cells in the case of Hodgkin s disease of the stomach note the hyperchromatic nuclei.



Fig 69 Malignant cells from the case of the neoplastic polyp of the pylorus note the nuclear cytoplasmic ratio and prominent nucleoli

CONCLUSIONS

Although our studies of the cytology of gastric sediment in patients with gastric symptoms number only 30, we are of the opinion that this method is promising in detecting early gastric and esophageal malignancy

We suggest this procedure as an adjunct to roentgenologic and endoscopic examinations in suspected lesions of the esophagus and stomach

At the conclusion of our study we sincerely hope that we can add a fourth and scientific method to the three methods previously quoted from Bockus for the early diagnosis of gastric malignancy

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formation Classifying the anemias according to the morphology of the erythrocytes, one can divide them into the commonly encountered groups Hypochromic microcytic anemia is most frequently found It is the result of iron deficiency, and in the malignancies this is usually secondary to chronic blood loss Next in frequency is the normochromic normocytic anemia which may be due to acute blood loss or to malnutrition as a result of anorexia, interference with digestion or interference with absorption The last, for example, may be due to the presence of diarrhea Blood destruction may also cause a normochromic normocytic anemia but in abdominal malignancy only an occasional case of acute hemolytic anemia has been reported Much has been written about macrocytic anemias in gastrointestinal malignancies but they are actually quite rare This type of anemia may be on the basis of a nutritional deficiency due to anorexia, infiltration of the gastric mucosa with a failure to produce the intrinsic factor, or to hepatic involvement The simple microcytic anemias are rarely encountered

ERYTHROCYTE MEASUREMENTS

The type of anemia ordinarily can be determined from the hemoglobin and erythrocyte count by the use of the color index This is determined by dividing the hemoglobin percentage by the percentage of erythrocytes The normal range is between 0 85 and 1 15 Unfortunately, this simple calculation leaves much to be desired due to the variability in the number of grams used for 100 per cent hemoglobin A much more satisfactory method is the use of the absolute values, the mean corpuscular volume and the mean corpuscular hemoglobin concentration These require the additional determination of the packed cell volume, the hematocrit It is well to be familiar with the normal values for these three determinations In the male the hemoglobin is 16 grams per 100 cc of blood, with a range of plus or minus 2 grams, and in the female 14 grams, with a range of plus or minus 2 grams For the purpose of the color index, 14 5 grams gives the best results The erythrocyte count in the male averages 5 4 million with a range of plus or minus 800,000, and in the female 4 8 million with a range of plus or minus 600,000 In calculating the color index 5 million is usually used The hematocrit in the male averages 47 per cent packed erythrocytes with a range of plus or minus 7 per cent and in the female it is 42 per cent with a range of plus or minus 5 per cent The average is 45 per cent packed erythrocytes The mean corpuscular volume is obtained by dividing the hematocrit by the red cell count in millions and multiplying by 10 The normal range is 87 plus or minus 5 cubic microns The mean corpuscular hemoglobin concentration is obtained by dividing the hemoglobin in grams by the hematocrit and multiplying by 100 The normal range is 34 plus or minus 2 per cent If the mean corpuscular volume is over 95 cubic microns, the erythrocytes are considered to be macrocytic If it is under 80 cubic microns, the erythrocytes are considered to be microcytic If the mean corpuscular hemoglobin concentration is over 30 per cent, the erythrocytes are considered to be normochromic and if under 30 per cent, hypochromic

USE OF THE BLOOD SMEAR

In a diagnostic problem this simple method of classification of the anemias on the basis of the color index or the absolute values is not adequate and the blood smears must be examined both as a check on the accuracy of the determinations and for the additional information which can be obtained. From the blood smear, one can differentiate a typical macrocytic anemia of the type seen in pernicious anemia from the macrocytic anemia of liver involvement. In the first type there is anisocytosis with macrocytosis, oval poikilocytosis and hypersegmented neutrophils. In the macrocytosis due to hepatic involvement there is usually no anisocytosis, the macrocytosis being generalized. There is also no poikilocytosis and no hypersegmentation of the neutrophils. Occasionally, there may be a hypochromic macrocytic anemia due to a deficiency of both iron and the erythrocyte maturating factor. At times one will encounter a regenerative macrocytosis. This occurs during rapid erythrocyte regeneration in hypochromic microcytic anemias when a large number of polychromatophilic macrocytes may be found in the peripheral blood. In the normocytic anemias one may find the presence of spherical microcytes or target cells which could not be detected by the absolute values. These findings may lead to further investigation and to a diagnosis of congenital hemolytic jaundice or sickle cell anemia. The other available hematologic determinations all help in the differential diagnosis and must always be correlated with examination of the blood smear.

LEUKOCYTE COUNTS

About one half of the cases of malignancy have a leukocytosis with some evidence of toxicity. This is accompanied usually by an increase in the sedimentation rate. In the differential diagnosis between carcinoma of the stomach and duodenal ulcer, and also in the differential diagnosis between carcinoma and pernicious anemia, some aid may be derived from the sedimentation rate. In rare instances of malignancy, a leukomoid reaction is found. Here either the leukocyte count is high enough or there are so many immature cells that leukemia is suggested. This is found at times, after hemorrhage or with metastasis to bone marrow or spleen. The malignancies which most frequently metastasize to bone are those of the prostate, kidney, thyroid and breast. At times, however, bony metastases are found with other malignancies. Metastatic bone lesions are visible ordinarily by x ray, but occasionally the leukemoid reaction is found before this occurs. The blood picture usually found with bone marrow metastases is of the type called a myelophthisic anemia or, by the English writers, a leukoerythroblastic anemia. Here, in addition to the leukocytosis and the presence of immature leukocytes, giant platelets are seen and there is evidence of erythrocyte regeneration with the presence of nucleated red blood cells, out of proportion to the degree of anemia found. Examination of the aspirated bone marrow ordinarily solves the problem when this situation is encountered. The reticulocyte count is valuable after a hemorrhage. When the bleeding has ceased, it should return to normal

Sometimes the *persistence of an increased reticulocyte count is the only evidence* of continued bleeding

BONE MARROW EXAMINATIONS AND OTHER PROCEDURES

Examination of the bone marrow is essential in any unexplained anemia, since it may lead one to the diagnosis of pernicious anemia, multiple myeloma, leukemia, aplastic anemia or one of the lymphoblastoma group If evidence of malignancy is found in the smears or sections of the bone marrow by the observation of tumor cells, one has conclusive evidence of metastasis This occasionally occurs before the metastases are visible roentgenographically There is a better chance of locating tumor cells if multiple aspirations are made The sternum, iliac crests and spinous processes of the lumbar vertebrae are readily available sites for puncture

Other hematologic procedures have their place and are to be used as indicated In the purpuras one derives aid from the bleeding, coagulation and clot retraction times, the platelet count and the tourniquet test The fragility test and the sickling test are indicated in hemolytic anemias

In the management of an anemic patient, it is well, if possible, to carry out the necessary diagnostic procedures before starting treatment Administration of iron, liver or transfusions may alter the blood and bone marrow so that it may be difficult to arrive at a satisfactory diagnosis If the patient is critically ill, at least a blood smear can be obtained prior to transfusion Treatment with iron or liver, whichever is indicated, is best If some error in diagnosis has been made, or if one is dealing with a combined type of anemia, the so-called dimorphic anemia, it will become obvious as recovery proceeds if only one hematinic agent has been used

In conclusion, a complete hematologic examination is important in the diagnosis of abdominal malignancy since, by excluding other causes for anemia, it frequently focuses attention where it properly belongs It may also disclose the true nature of the disease in lymphoma, leukemia or multiple myeloma and occasionally aid in prognosis by disclosing metastases before they are visible grossly or by x-ray

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THE PRESENT MANAGEMENT OF CARCINOMA OF THE STOMACH

L KRAEER FERGUSON, M D

Carcinoma of the stomach is looked upon as a most discouraging disease In the minds of many physicians the possibility of cure is so slight that they hesitate to recommend radical surgery This point of view may have been justified in years past, but with advances in surgical preparation and post operative care with the advantages of professional anesthetists, and with new operative technics the outlook for the patient with gastric cancer is much brighter

Gastric carcinoma is one of the most common causes of deaths from malignancy It is estimated to be the cause in 20 to 30 per cent of the deaths from carcinoma It is probably the most common single malignancy in males and second only to those of the reproductive organs in the female According to Dublin[1] gastric carcinoma is responsible for about one third of all deaths from carcinoma in white males and one fifth in white females

It is recognized by all that complete surgical removal is the only treatment that offers any chance of cure in cancer of the stomach In order to remove a cancer completely it must be attacked surgically before irremovable spread of the tumor has taken place Hence the necessity for early diagnosis in gastric cancer Because the early symptoms of gastric carcinoma are so indefinite, and because such a large percentage of patients reach the surgeon too late for curative surgery efforts have been made to discover cancer of the stomach in its earlier phases Mass x ray seemed an obvious method St John Swenson and Harvey examined 2413 patients over fifty years of age and found three unsuspected malignancies of the stomach two carcinomas and one lymphosarcoma an incidence of 1 24 per 1000 Dailey and Miller[3] examined 500 normal males over forty and in this group were found one benign ulcer one polyp and one case of antral gastritis Wangensteen[4] narrowed his selection to patients over fifty years of age free of digestive complaints who were achlorhydric after histamine stimulation In 464 patients 15 patients were found to have gastric polyps There were three cases of undetected gastric carcinoma only one of these was early and this was missed by the x ray and found incidentally when the patient was operated upon for a cecal carcinoma which was demonstrated in the x ray study In a later report from the University of Minnesota using the same factors for selection, State[5] found 7 gastric cancers and 25 gastric polyps in 1111 gastrointestinal studies It is apparent that mass x ray examinations can hardly be looked upon as a method that will pick up large numbers of early cancers of the stomach

Improvement in results must come from education of physicians to be on the alert to recognize the early symptoms of the disease Eliason and Welty[6] found that delay in treatment averages five months from the time of first

symptoms to the time of treatment, and they found the delay was greater from the time the patient was first seen by a doctor to the time of operation, than from the appearance of first symptoms until the first visit to a doctor Lahey, Swinton and Peelen[7] report an average duration of symptoms of eight months plus Can this delay be reduced in the hope that more gastric cancers can be recognized in the early phase of the disease?

FACTS KNOWN CONCERNING GASTRIC CARCINOMA

It is a disease appearing primarily in late adult life Marshall[3] points out that 73 per cent of the patients seen at the Lahey Clinic with carcinoma of the stomach are over fifty years old and 93 per cent of their cases appeared in patients over forty It is a disease that appears more often in males than females, the ratio being slightly greater than four to one

The symptoms of gastric cancer so often repeated in the literature on the subject are usually those produced by advanced disease Nausea, vomiting, anorexia, weight loss, anemia, the appearance of a mass in the epigastrium, are symptoms of a cancer with obstruction, ulceration or extensive growth, producing secondary systemic effects Pack and McNeer[9] point out that simple *indigestion, a change in a previous sense of well being, a "stomach conscious* ness," slight anorexia or fullness after meals, and a mild anemia are significant symptoms, especially if they first appear after forty years of age and in a male A barium meal x-ray study is probably the most reliable single diagnostic method, and should be made even though the symptoms may seem relatively trivial to the patient Only by an investigation of early symptoms can early carcinoma be detected

LESIONS THAT SHOULD BE LOOKED UPON AS PRECANCEROUS

Achlorhydria is well known as a common finding associated with gastric carcinoma, but in State's study of 1111 patients with achlorhydria he found only 7 cases of carcinoma and 25 of gastric polyps In a study of 79 patients who developed carcinoma over an average period of six years, Comfort, Butsch, and Eusterman[10] noted that the incidence of achlorhydria increased from 38 to 64 6 per cent They point out that the chronic gastritis associated with gastric cancer may be responsible for this fall in gastric acidity As far as our knowledge goes today, achlorhydria cannot be looked upon as a finding that suggests preclinical cancer, and it is well known that many cases of gastric cancer do not show achlorhydria

Rigler, Kaplan and Fink[11] in studying more than 200 patients with *pernicious anemia* found that 8 per cent had carcinoma and 7 1 per cent benign gastric polyps This much increased incidence of gastric tumors in patients with pernicious anemia they looked upon as etiologically significant and they recommend biannual routine x-ray study of patients with primary anemia

Gastric polyps, like polyps elsewhere in the intestinal tract, are looked upon as prone to undergo malignant degeneration The relatively high incidence of polyps associated with achlorhydria and pernicious anemia has been pointed out above Stewart[1] found 28 per cent of polyps examined to be malignant,

and Benedict and Allen[13] an incidence of malignancy as high as 41 2 per cent Such figures indicate the potentially malignant nature of gastric polyps, and they suggest careful observation or perhaps better, removal of the polyp as a prophylactic measure

GASTRIC ULCERATION AND MALIGNANCY

Approximately one third of patients with gastric carcinoma give a history which suggests gastric ulcer, and the problem of the roentgenologist and the gastroscopist is to differentiate morphologically those ulcers which are malignant from those which are benign Hardt et al [14] and Benedict[15] believe that the combination of roentgenology and gastroscopy gives the most accurate results Hardt found 98 per cent of carcinomas correctly diagnosed by combining the two methods The study of stained cells obtained by gastric aspiration is an added method of differential diagnosis

The location of the ulcer is believed to be of some significance in a differentiation between benign and malignant ulceration It is generally thought that ulcers of the prepyloric area and on the greater curvature are malignant in a high percentage of cases This problem was subjected to a critical analysis by Smith and Jordan[16] in 258 operated cases They found an incidence of malignancy in gastric ulcerations as follows greater curvature 60 per cent, fundus 50 per cent, prepylorus 17 per cent, corpus and lesser curvature 17 per cent Allen s[17] figures from a ten-year survey of records at the Massachusetts General Hospital are somewhat at variance He showed that 65 per cent of lesions in the prepyloric area (2 cm from the pylorus) were malignant Most lesions of the fundus and greater curvature are malignant 20 per cent of lesions of the anterior and posterior walls and 10 per cent of lesions of the lesser curvature are malignant Allen pointed out that most diagnostic errors occur with lesions of the lesser curvature where at least half of the malignant gastric lesions are found

Another question as yet still unanswered concerns the tendency of benign ulcers to undergo malignant degeneration This problem perhaps can never be solved but a studied opinion can be based upon experience Ransom[19] believed that about 5 per cent of benign ulcers undergo malignant degeneration if they are resistant to nonsurgical measures Jordan[16] believes that malignant changes are prone to occur in recurrent gastric ulcer In 98 cases of gastric ulcer followed five years or more, 40 8 per cent had recurrences She concludes that recurrent ulcerations must be an indication for resection

A final consideration in this ulcer versus carcinoma problem concerns our ability to differentiate ulcer from carcinoma even with the best of studies and wide experience Allen[17] states that 14 per cent of patients treated for benign ulcer at the Massachusetts General Hospital were proved to have carcinoma of the stomach Marshall[8] reports from the Lahey Clinic 131 patients operated upon for benign ulcer, of whom 26 had malignancies—an error of 19 8 per cent Wangensteen[4] reports an error of approximately 10 per cent Jordan[16] states that of 44 operated malignant ulcers, 23 were considered to be benign after the initial clinical and roentgenologic survey had been com-

pleted, and of 211 operated benign ulcers, 89 or 42 1 per cent were operated upon with the diagnosis of carcinoma or probable carcinoma This frequency of uncertainty or error in diagnosis, even in the best hands, has led what Dr Eusterman[10] describes as "some representative, otherwise conservative surgeons' to advocate immediate operation on every ulcerous gastric lesion Although the risk of operation in good hands is slight, and the disability produced by gastric resection is not great, still there would seem to be reason for individualizing each case of gastric ulceration The consensus of surgical opinion would seem to be that all gastric ulcers should be considered potentially malignant This potentiality increases if the patient is a male, over fifty, if there is no free hydrochloric acid, if the ulcer is large, or if it is located in the prepyloric area or greater curvature, or if it is recurrent or chronic on the lesser curvature If any of these conditions are present the index of suspicion of malignancy should be high If several are combined in the same patient the probability of malignancy is increased and early operation should be advocated

Gastric ulcers not fulfilling these conditions may be treated conservatively but if roentgenologic healing and clinical improvement do not occur within two to three weeks with intensive medical treatment, surgical exploration should be seriously considered

PRINCIPLES OF THE OPERATION FOR GASTRIC CARCINOMA

The operation for carcinoma of the stomach follows the same principles which have been laid down for operation for cancer elsewhere in the body, namely, removal of the primary growth, along with the areas of lymphatic spread, and removal of other adjacent organs to which the tumor may have spread by continuity In the application of these principles the cancer bearing area of the stomach is removed The lymphatic spread of cancer in this area is along the nodes at the left gastric artery, in the area of the pylorus and the head of the pancreas, and to the greater omentum Hence in performing a radical operation for cancer of the stomach, the stomach is removed from the pylorus proximally to the cardiac orifice on the lesser curvature, the omentum is dissected from the colon, and the entire greater omentum and gastrocolic omentum are removed with the greater part of the greater curvature If the tumor has spread by contiguity to the underlying pancreas or to the adjacent colon or liver, these areas are also removed with the tumor In most cases enough of the stomach may be preserved to reform the continuity of the intestinal tract by a gastrojejunostomy

When a subtotal resection of the stomach does not remove all of the cancerous tissue, a total gastrectomy may be performed In the opinion of most surgeons this radical resection is not necessary in most cases of carcinoma Shields Warren (quoted by Marshall[9]) has investigated 122 cases at post mortem who had had previous gastric resection for carcinoma In 23 there was a recurrence in the gastric stump In 99 recurrence appeared elsewhere The added morbidity and mortality with total gastrectomy would not seem to justify this operation routinely in an attempt to remove carcinoma of the

stomach From a pathologic point of view it appears that carcinoma does not extend horizontally along the wall of the stomach for a great distance, and that, therefore, a resection of the stomach wall an inch and a half or two inches above the upper margin of the visible and palpable growth would satisfy all radical considerations In cases with carcinoma in the area of the cardiac orifice and fundus, the operation may best be performed through the chest or through a combined abdominothoracic incision This is recommended because the approach is easier and more direct and because of the lymphatic spread upward along the lower esophagus in such growths We have seen several cases in which the only palpable metastatic involvement from a carcinoma of the cardiac orifice was into the greater omentum Hence it is recommended that even though a transthoracic approach is used the greater omentum should be excised

In operating for cure of gastric cancer the surgeon need not necessarily be discouraged by the fact that the tumor has penetrated the serosa and has involved adjacent organs by continuity If these organs are removable, it is possible to obtain an excellent result Pack and McNeer[9] report 16 cases of gastric cancer involving adjacent organs and of these, 8 were living and well five years later Of these 6 patients were shown to have metastatic cancer in lymph nodes removed with the gastric tumor These authors point out that removal of gastric cancer which invades or is adherent to liver, pancreas spleen or transverse colon is feasible and worth while They believe that a high percentage of five-year cures may be obtained even if metastases occur in perigastric lymph nodes

The question may be rai ed at the operating table in patients with irremovable metastasis as to whether any surgery should be done It is the opinion of most surgeons that the removal of an obstructing or ulcerating tumor of the stomach is the best form of palliation It is questionable whether a simple short circuiting operation such as gastroenterostomy has any value in the palliative treatment of gastric carcinoma

OPERABILITY OF GASTRIC CARCINOMA

Figures on the operability of patients with gastric carcinoma are available from many of the large clinics (Table 5) Pack and McNeer[9] in a recent report from the Memorial Hospital show a gradual increase in operability from 51 8 per cent of their total cases in 1916 to 1930 to 82 7 per cent in 1942 to 1946 A recent report[19] from the University of California shows an operability rate of 69 2 per cent A review of the literature would seem to show that from one half to one third of patients with gastric cancer are judged inoperable by the time they see the surgeon

Of the patients who are operated upon approximately 50 per cent may have a gastric resection performed Pack and McNeer report a resectability rate of 48 1 per cent of the cases subjected to operation Bell s figure is 49 7 per cent Marshall from the Lahey Clinic reports resectability in 48 2 per cent of operative cases Walters et al [0] report resectability of 53 8 per cent Wangensteen resected 90 per cent of the gastric cancers operated upon

In our own small series of 31 patients during the last three years, operations have been performed upon 29 or 93 5 per cent Of these a gastric resection was possible in 24 patients, a resectability rate of 82 8 per cent of patients operated upon This represents a resectability rate of 77 4 per cent of all cancer

Other figures in the literature show a gradually increasing operability and resectability as compared with earlier years, indicating that a larger number of patients are being given a chance for survival

Table 5 Operability and Resectability of Gastric Cancer

	TOTAL CASES	OPERABILITY		RESECTABILITY		
		No	Per Cent Total Cases	No	Per Cent Operated Cases	Per Cent Total Cases
Pack and McNeer	405	335	82 7	161	48 1	39 8
Bell	540		69 2		49 7	34 4
Maimon and Palmer	466		83 5		43 5	
Ferguson	31	29	93 5	24	82 8	77 4

OPERATIVE MORTALITY FOR CANCER OF THE STOMACH

Has the tendency to increase the number of gastric resections in the treatment of carcinoma increased the hazard? Is the operative mortality prohibitive? Recent figures from representative clinics are as follows Pack and McNeer[9] with 161 cases of gastric resection record an operative mortality of 21 7 per cent This includes, however, 33 cases of total gastrectomy, with a mortality of 36 4 per cent, and 36 cases of resection of the cardia, with a mortality of 38 9 per cent There were 92 subtotal resections for cancer, with 9 deaths or 9 8 per cent mortality Bell[19] reports an operative mortality of 11 9 per cent from the University of California, and from the Lahey Clinic the figure is given as 6 per cent At the Mayo Clinic [0] for the year 1947, the mortality rate for partial gastrectomy for carcinoma of the stomach was 6 4 per cent, and for total gastrectomy was 5 3 per cent In our own series of 29 operative cases there were no operative deaths This includes 24 gastric resections, one of which was a total resection It would appear that the hazard of gastric resection for gastric carcinoma is not excessive, and mortality of even 20 or 30 per cent for total gastrectomy or transthoracic gastrectomy would not seem to be high since the patient is doomed to a fatal outcome without operation

FIVE YEAR SURVIVAL FOLLOWING RESECTION FOR GASTRIC CARCINOMA

We are indebted to the larger clinics for the results of follow-up examinations of a large series of patients In the older literature it was estimated that

five year survivals following resection for gastric carcinoma might be in the neighborhood of 20 to 25 per cent Custer [1] reported 41 patients with an established diagnosis of carcinoma who were submitted to gastric resections After five years 27 6 per cent were alive and 18 75 per cent were alive after eight years A group of 28 patients who refused operation were all dead at the end of three years Pack and McNeer[9] who quote the latest figures from the gastric service of the Memorial Hospital show that 34 7 per cent of 75 survivors of gastric resection lived for five years without evidence of recurrence One hundred gastric resections were performed during the period studied with an operative mortality of 25 per cent, which represents a five-year survival of 26 per cent of the patients who had gastric resection a five year survival of 6 1 per cent of all patients with gastric carcinoma who were operated upon, and 0 3 per cent of all the cases of carcinoma seen during the period of study This report also states justly that when later studies are made it will be shown that the present increase in operability and resectability will have increased the number of five year survivals Welsh and Allen[7] report that 24 patients lived five years or more, of 115 operative survivors of gas trectomy This represents a five-year cure of 20 1 per cent of those surviving gastrectomy Four survivors with proven metastasis lived five years or more (5 per cent) Twenty of 42 survivors without metastasis lived five years or more (30 per cent)

Pack and McNeer[9] made a study of various factors which influence the five year survival rate They were surprised to find that the average duration of symptoms before operation in those who survived resection was the same, 9 7 months, in those who lived five years or more and in those who lived less than five years They pointed out that of their patients who lived five years or more, 62 9 per cent did not have metastasis in perigastric lymph nodes, but they were surprised to find that in 30 8 per cent of the cured cases cancer was demonstrably present in the excised lymph nodes

COMMENTS

Gastric carcinoma is a disease which is curable only by surgical removal of all of the carcinoma This is possible if the disease is recognized in its early stages A knowledge of the characteristics and nature of the disease helps to raise the index of suspicion of gastric carcinoma It appears usually in patients past forty, most commonly in males The early symptoms are vague, the most critical diagnostic method is the x ray examination Most patients with a gastric ulcer should be suspected of having carcinoma

Improvements in pre and postoperative care, anesthesia and various new operative technics have increased the operability for this disease and have per mitted resection of an increasing number of gastric cancers Subtotal resection is usually sufficient in most cases of gastric carcinoma but it is necessary to remove also the areas of lymphatic spread including the greater omentum Total gastrectomy and transthoracic gastrectomy are other operations available in indicated cases

These surgical procedures can be carried out with a relatively low mor-

tality The figures available at this time would show an average of 30 per cent of five-year survivals in patients who survive gastrectomy The results are best in cases in which no metastasis was present, but even with demonstrated metastasis to lymph nodes or extension to adjacent organs, five year survivals may be obtained by radical extirpation of the tumor

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PROGNOSIS IN GASTRIC MALIGNANCY BASED UPON THE GROSS AND MICROSCOPIC CHARACTER OF THE LESION

ANTONIO VALDES-DAPENA, M D

GROSS CHARACTERISTICS

Grossly carcinoma of the stomach manifests itself in one of three major types

1 Polypoid tumor
2 Ulcer
3 Diffuse type

The *polypoid* type of tumor may vary from a small, pink, symmetrical, hemispherical or discoid mass, well circumscribed and attached to a normal

appearing mucosa, to a huge, irregular, cauliflower like mass of many colors from light red to purplish black, necrotic, surrounded by an obviously infiltrated mucosa These variations represent different stages of a single process

The *ulcerated* or ulcer like cancer results from necrosis of a previously fungating growth occasionally from focal necrosis of a diffuse infiltrating tumor This ulceration may have occurred more or less early Such an ulcer arising upon a preexisting neoplastic process could be called a ' pathologic ulcer Some of these lesions still show extensive papillary growth along their edges

In this discussion we cannot go into the matter of malignant transformation of peptic ulcers of the stomach, suffice it to say that the great majority of malignant ulcers are not the result of such a transformation

Most classifications, practically all the better known ones, establish two groups of ulcerating carcinomas, one which is a clearly defined ulcer and one in which there is irregularly demarcated ulceration The latter, we feel, is really a transitional form The object of the present classification into three groups instead of four is to point out the main pure types acknowledging from the outset that most tumors will show transition from one type to the other It is well to emphasize as Schindler does that transformation occurs always in the direction of the diffuse type

The majority of cancers of the stomach belong in the group of ulcerating and infiltrating carcinomas, each tendency being manifested in varying degree

The *diffuse* type of carcinoma is a special form resulting from the fact that the stomach contains a very rich lymphatic network running parallel to the surface This network is described by Konjetzny as being formed by four parallel groups of vessels mucosal submucous, intramuscular and subserous with corresponding intercommunicating trunks running perpendicular to the wall Thus the spread of the cancer cells is facilitated in the horizontal sense which results in extensive diffusion of the tumor throughout the wall, while the vertical growth toward the mucosa or the serosa may lag far behind Why some tumors take full advantage of these conditions and others do not is not known However it must be remembered that most of them do grow in this fashion to a greater or lesser degree Papillary tumors are definitely in the minority pure papillary tumors representing less than 5 per cent of all forms

The diffuse gastric carcinoma is characterized grossly by a rather uniform thickening of the submucosa and the muscular coat while the mucosa be comes coarse flattened and may show irregular shallow ulcers

PROGNOSTIC EVALUATION

There is general agreement that a polypoid tumor of the stomach conveys a better prognosis than any other type A well circumscribed ulcerated tumor is next in line The diffuse carcinomas are the most deadly There is then a distinct gradient of malignancy toward the diffuse type In Palmer s series of 377 patients of whom 28 survived for five years all but 2 of the survivors had well circumscribed tumors

The reason for this is to be found in the mode of growth While the bulky

polypoid masses do all their growing out of a relatively small area which they infiltrate through and through, they expend a good deal of their capacity for growth in an outward push into the lumen where they are at least partly amputated by necrosis The diffuse tumors, on the other hand, whether pure or combined with ulceration extend along the stomach wall, their actual area of involvement can not be accurately estimated, which makes the resection of the tumor a blind procedure

Size of the Tumor The bulk of the tumor can be a most misleading prognostic sign The largest masses are provided by the papillary tumors growing mainly into the lumen, and yet these are the least malignant It is interesting that in a study of 30 cases of five-year survival, fully 25 per cent of the patients had a palpable mass when first seen

Location of the Tumor More than half of the carcinomas of the stomach are located in the region of the antrum A great many of them involve the lesser curvature in that area Carcinomas of the greater curvature and fundus are less common Unfortunately the latter are more commonly attended by a better prognosis The distribution and richness of lymphatic networks is such that the more common growths of the lesser curvature and the antral regions will invade more lymphatic trunks and at an earlier date than the fundal and greater curvature tumors

Involvement of Adjacent Organs This element governs the prognosis to a great degree The prognosis of tumors localized to the stomach is almost three times as good as that of tumors associated with invasion of lymph nodes Of 919 resections without nodal involvement 43 per cent resulted in five-year survival (Willis) as against a 16 per cent survival rate among 1049 cases with lymph node metastases It is well known that residual portions of carcinoma inevitably and knowingly left in the body at operation may not prosper, or may grow so slowly as never to become a factor in the patient s survival, so that even extensive invasion of adjacent organs does not necessarily mean that the prognosis is hopeless

MICROSCOPIC CHARACTERISTICS

The following major microscopic types can be distinguished

1 Papillary adenocarcinoma
2 Well differentiated nonpapillary adenocarcinoma
3 Solid carcinoma
4 Scirrhous carcinoma
5 Anaplastic or poorly differentiated types

The architecture of *papillary adenocarcinoma* is such that a section taken from it might be interpreted as part of a benign polyp The nuclei may be in perfect arrangement along the base of the cell and show uniformity of size and staining quality This type is not frequent and is found exclusively among the polypoid tumors On the other hand, polypoid tumors may show other microscopic appearances in their deeper portion

Adenocarcinomas with a distinct glandular arrangement and fairly uniform

cellular patterns are quite common Any type of gross lesion may show this type of microscopic architecture either in part or throughout

Solid carcinoma is represented by sheets of cells with no attempt at gland formation yet showing a fair degree of cellular uniformity The cells may be all large or they may be small, the latter type being suggestive of and even difficult to differentiate from argentaffin carcinoma The solid type of growth is found almost invariably in ulcerative or diffuse growths

Although *scirrhous carcinoma* is not exclusively found in the stomach it is more characteristic of this organ than of any other It is made up of a very prominent stroma of dense fibrous tissue in which one may see infiltrating strings of neoplastic cells in single file or even single cells quite distant one from another At first sight and under low magnification such tumor tissue might well be mistaken for a low grade chronic inflammation or scar tissue Close inspection of the cells, however leaves no doubt that they are malignant cells Many of them show giant nuclei others carry large vacuoles in the cytoplasm— signet ring cells The mucosa which may be preserved over areas of advanced growth looks washed-out and atrophic, with many signet ring cells scattered through it

Anaplastic or undifferentiated carcinoma of the stomach may simulate lymphosarcoma or spindle cell sarcoma It may likewise show an infinite variety of cellular types and architectural pattern When multiple sections are examined the glandular nature of the tumor can often be detected in places

Other pertinent remarks in regard to microscopic features of gastric carcinoma should include a reference to the mucoid type This is an adenocarcinoma with a noticeable accumulation of mucus in the acini to the point of almost complete replacement of the cellular components Some authors have ascribed a particularly poor prognosis to this type We share the feeling of others that a pure form of mucoid carcinoma is too rare to afford opportunities for evaluation

Another interesting observation has been that tumors with marked leukocytic infiltration are likely to be less malignant The inference is that the inflammatory reaction might represent a defensive gesture on the part of the organ

CORRELATION OF GROSS AND MICROSCOPIC TYPES

Except for the association of gross and microscopic papillary characteristics there is no actual correlation Diffuse carcinomas which would suggest a scirrhous type of microscopic architecture are not predominantly scirrhous One study brought forth 33 per cent of adenocarcinomas among a group of diffuse infiltrating cancers (Konjetzny) The most common gross type the mixed ulcerated and infiltrated tumors, show all microscopic patterns except the papillary form

Grading of tumors We believe that only the extreme grades are of practical importance in prognosis A very orderly appearance is consistent with slow growth and delayed extension while the wildly anaplastic microscopic pic

polypoid masses do all their growing out of a relatively small area which they infiltrate through and through they expend a good deal of their capacity for growth in an outward push into the lumen where they are at least partly amputated by necrosis The diffuse tumors, on the other hand, whether pure or combined with ulceration extend along the stomach wall, their actual area of involvement can not be accurately estimated, which makes the resection of the tumor a blind procedure

Size of the Tumor The bulk of the tumor can be a most misleading prognostic sign The largest masses are provided by the papillary tumors growing mainly into the lumen, and yet these are the least malignant It is interesting that in a study of 30 cases of five-year survival fully 25 per cent of the patients had a palpable mass when first seen

Location of the Tumor More than half of the carcinomas of the stomach are located in the region of the antrum A great many of them involve the lesser curvature in that area. Carcinomas of the greater curvature and fundus are less common Unfortunately the latter are more commonly attended by a better prognosis The distribution and richness of lymphatic networks is such that the more common growths of the lesser curvature and the antral regions will invade more lymphatic trunks and at an earlier date than the fundal and greater curvature tumors

Involvement of Adjacent Organs This element governs the prognosis to a great degree The prognosis of tumors localized to the stomach is almost three times as good as that of tumors associated with invasion of lymph nodes Of 919 resections without nodal involvement 43 per cent resulted in five-year survival (Willis) as against a 16 per cent survival rate among 1049 cases with lymph node metastases It is well known that residual portions of carcinoma inevitably and knowingly left in the body at operation may not prosper, or may grow so slowly as never to become a factor in the patient s survival, so that even extensive invasion of adjacent organs does not necessarily mean that the prognosis is hopeless

MICROSCOPIC CHARACTERISTICS

The following major microscopic types can be distinguished

1 Papillary adenocarcinoma
2 Well differentiated nonpapillary adenocarcinoma
3 Solid carcinoma
4 Scirrhous carcinoma
5 Anaplastic or poorly differentiated types

The architecture of *papillary adenocarcinoma* is such that a section taken from it might be interpreted as part of a benign polyp The nuclei may be in perfect arrangement along the base of the cell and show uniformity of size and staining quality This type is not frequent and is found exclusively among the polypoid tumors On the other hand, polypoid tumors may show other microscopic appearances in their deeper portion

Adenocarcinomas with a distinct glandular arrangement and fairly uniform

have a cure of a widespread infiltrating carcinoma although Dr Pack and Dr McNair report that in 16 cases of carcinoma which had spread by extension so that other organs were involved and necessitated resection of other organs, they had 8 five-year cures

Question What is your opinion of total gastrectomy in the cure of gastric carcinoma? There are some clinics now that are adopting total gastrectomy as the operation of choice for any carcinoma of the stomach What is your opinion about that?

DR FERGUSON Of course the operation that we prefer to perform for carcinoma is one which gives us the best chance of removing all of the carcinoma, and in various clinics, notably in Baltimore they believe that in order to remove all chance of recurrent carcinoma and to remove all of the lymphatic drainage along the left gastric artery, it is better to do a total gastrectomy than a partial or subtotal gastrectomy This view is not held by all surgeons for various reasons In the first place, a total gastrectomy increases the mortality tremendously You saw the mortality figures from Memorial Hospital—for simple subtotal gastrectomy, 9 8 per cent for total gastrectomy 36 4 per cent Secondly the patient is not nearly as comfortable postoperatively which of course, is not a compelling reason but it s one to be considered certainly in taking out the stomach And the third reason is because carcinoma does not recur in the stump of the stomach—it recurs elsewhere Now I d like to quote some figures to you that show what the percentage is

Shields Warren in some unpublished figures quoted by Dr Marshall says that he autopsied 122 patients who had a subtotal gastrectomy for carcinoma of the stomach Of this group 23 had recurrences in the gastric stump as compared to 99 in which recurrence was elsewhere In other words, the incidence of recurrence in the gastric stump is relatively low as compared to the recurrences elsewhere so that there is really no particular advantage in a total gastrectomy for carcinoma in its commonest location—i e in the pre pyloric area or antrum Obviously in diffuse carcinoma of the linitis plastica type nothing can be done to aid these patients except a total gastrectomy

Total gastrectomy is done also for carcinomas of the fundus or the cardiac end of the stomach, but in most of these cases, a subtotal gastrectomy gives good results

Question What are the indications for surgery in chronic gastritis? The question was asked of the surgeon

DR FERGUSON The indication for operation in chronic gastritis, as far as the surgeon is concerned is the opinion of the gastroenterologist I would like to say one word or two more I don t think there is any question but that patients with chronic gastritis must be carefully watched and should be considered potentially malignant Some who are particularly interested in the question of gastric carcinoma believe that carcinoma never arises from normal mucous membrane, therefore, any abnormality of the mucous membrane one of the commonest of which in the older age group is chronic gastritis, should be looked upon as a potentially premalignant lesion On the other

tures suggest a more dangerous tumor Basing a prognosis upon a classification of intermediate grades will probably result in error as often as it will prove correct

SUMMARY

Papillary and well localized tumors whose growth is mainly vertical rather than horizontal are easier to resect and more tardy to extend and metastasize

Other than the polypoid tumors which are usually microscopically well differentiated papillary adenocarcinomas, there is little or no correlation between gross and histologic types

The degree of histologic differentiation may play a part in prognosis after the gross characteristics have been considered

Tumors of the greater curvature and fundus have a better prognosis in general

The size of the tumor can be used as an index of prognosis only when the morphologic character of the tumor is taken into consideration

QUESTIONS AND ANSWERS

Question Dr Imbriglia, is this method of yours applicable or of value only for the growth which has undergone ulceration?

Dr Imbriglia No sir, this method is applicable to any lesion which is exfoliating cells Ulceration of the growth with secondary infection and the subsequent outpouring of inflammatory cells causes the greatest difficulty in correct interpretation

Question Can you distinguish the rapidly infiltrating type of carcinoma from the more slowly metastasizing neoplasm?

Dr Imbriglia No sir, we can only make a diagnosis of the presence of malignant cells *However, it is possible to differentiate malignant squamous* cells from malignant cells derived from a gastric carcinoma

Question Dr Ferguson, what is the overall percentage of five-year cures in a mixed group of gastric carcinomas?

Dr Ferguson The overall percentage is approximately 5 to 6 per cent and I believe that varies somewhat from clinic to clinic, but it s not much better now than it was some years ago I mean to say that even with more radical operations, we have only a few more five-year cures We have much better palliation and many more people live longer in comfort with more radical surgery than they did before, but as Dr Valdes-Dapena said probably most of the cases of carcinoma of the stomach that are cured are those of malignant degeneration of polyps, or those which have small carcinomatous ulcers operated on with a diagnosis of benign ulcer It is relatively rare, I think, for us to

cause we thought that it was probably carcinoma An extensive change was noted throughout the entire stomach At operation only a biopsy of the stomach was taken The process has completely subsided and the patient is entirely well In another instance of extensive gastritic changes throughout the stomach with multiple ulcerations, the patient is likewise well By x ray the mucosa now appears perfectly normal Many believe that such a change cannot occur but it does occur I know of no indication for surgery for gastritis alone

DR BOCKUS Now, Dr Monaghan suppose this patient with severe hypertrophic gastritis with erosions was having a severe hemorrhage every nine months or a year—would that be an indication for resection of the stomach or is there some other more adequate treatment for erosive gastritis with exsanguinating hemorrhages Would you remove that stomach, or what would you do?

DR MONAGHAN I have not recommended operation Have you seen anyone die from an erosive gastritis?

DR BOCKUS Yes in a patient following operation, otherwise we would never have made the diagnosis It was an instance of exsanguinating hemorrhage with hematemesis and melena We fought for three days, maintaining the patient s blood volume with blood transfusions We hesitated about operation as the patient had a very slightly palpable spleen but without evidence of liver dysfunction Dr Walter Lee did a large subtotal gastric resection This patient had advanced hypertrophic gastritis with nine large erosions by actual count in the stomach The bleeding continued after the resection and the patient succumbed We presumed that there were other erosions in the duodenum There was nothing to suggest a defect in blood clotting

Is there no other treatment that you can suggest for this situation?

DR MONAGHAN In the cases I have seen gastroscopically because of the diffuse character of the erosive gastritis, a total gastrectomy would have been required

DR BOCKUS And how about the duodenal bulb? Would it have to come out too?

DR MONAGHAN Yes, I suspect so It is for that reason that I would not knowingly recommend operation

DR BOCKUS How would you treat such a patient? By irradiation?

DR MONAGHAN No

DR BOCKUS How about a vagotomy? What would that do to such a stomach?

DR MONAGHAN I ve had no experience with it but there have been a few cases in which vagotomy has been done for erosive gastritis without effect

DR BOCKUS Are you familiar with the 11 cases that Dr Moore of Boston has reported of so called silent gastric hemorrhage without any recurrence after vagotomy? I presume that some of these patients may not have had ulcer perhaps some were examples of erosive gastritis One of my reasons for asking Dr Hollander the question this morning was the thought that perhaps after vagotomy mucin secretion might increase tremendously forming a pro

hand, we do not believe that any patient with chronic gastritis without evidence suggesting concomitant malignancy should be operated on for carcinoma and a gastric resection performed

DR BOCKUS I should like to go on record as disagreeing with those who make the statement that we have proof that the great majority of patients with gastric carcinoma have had an antecedent gastric lesion I would go on record very strongly as being against that viewpoint There is no proof to indicate that the great majority of patients with gastric carcinomas have had antecedent gastric disease There isn t any doubt but that an odd patient with atrophic gastritis, with polypoid disease of the stomach or with gastric ulcer will develop gastric carcinoma, but the great bulk of gastric carcinomas undoubtedly develop in the absence of previous mucosal disease

I should like to hear what Dr Monaghan has to say about the indications for operation in chronic gastritis

DR JAMES F MONAGHAN It is my belief, also, that the statement that carcinoma doesn t occur except in a previously diseased and inflamed membrane whether it's atrophic or hypertrophic is entirely without proof at present For instance, I should like to mention a report which I believe emanated from the Mayo Clinic several years ago Careful histologic studies were made of a large number of stomachs resected for cancer They found that the stomachs showing histologic evidence of gastritis were often obstructed or had been subjected to a lot of trauma as a result of the carcinoma Those stomachs showing no obstruction or extensive malignant invasion exhibited no unusual gastritic finding There s one other thing to which I should like to take exception I don t think that we can be sure that polyposis of the stomach frequently becomes malignant We have not had too many patients of this type to follow, but we have a slide demonstrating gastric polyps in a patient who has been followed for five years The patient was followed longer than that before she died These polyps can be seen quite well They were seen gastroscopically She was not operated upon because of a cardiac condition To our knowledge, she had these polyps for seven years and at autopsy they were entirely ordinary benign polyps We have now a three-year follow up on the patient mentioned by Dr Finkelstein who was not operated upon because of heart disease I am not convinced that polyposis of the stomach frequently undergoes malignant change

DR BOCKUS I m going to have to insist that you answer the question We will have very little opportunity to discuss chronic gastritis The question specifically had no bearing on carcinoma The question was "When do you recommend operation for chronic gastritis?

You know the intent of the question We see patients with chronic gastritis with or without duodenal ulcer who have intractable symptoms Should operation ever be considered?

DR MONAGHAN I misinterpreted the question I thought that perhaps the question was aimed particularly at the potentiality of the gastritic stomach becoming malignant For gastritis itself I would never operate on the patient In one case of extensive gastritis subjected to operation we operated be-

Peptic Ulcer

tective layer on the stomach I wondered whether this might play some role in the absence of recurrences in Moore s patients

DR MONAGHAN I am not sure that his cases have been followed long enough to mean anything I know of only two cases of proved erosive gastritis in which vagotomy was done The erosive gastritis was noted gastroscopically after operation

DR BOCKUS Wouldn't you relent just a little and consent to give irradiation to a patient with extensive hypertrophic erosive gastritis?

DR MONAGHAN Don t forget that I ve mentioned two cases in which good results were obtained without resection, irradiation or vagotomy

DR BOCKUS You mean you can cure all of them without resort to any of these measures?

DR MONAGHAN Yes, I think that all cases of erosive gastritis are on a psychosomatic basis

ROLNTGEN DIAGNOSIS OF POSTBULBAR DUODENAL ULCER

ARTHUR FINKELSTEIN, M D

Before discussing postbulbar ulcers, it will first be necessary to define what is meant by the term "bulb Bulb does not mean merely the proximal bulbous portion of the duodenal cap It is now generally agreed that the term duodenal bulb is synonymous with duodenal cap, and that both terms refer to the entire first portion of the duodenum The bulb starts at the pyloric canal and terminates in average cases 4 or 5 cm distally at the angle' which is usually prominent When 'the angle of the juncture of the first and second portions of the duodenum is not easily identified by its external configuration (angularity, change in direction decrease in caliber) it is usually recognizable by the change in mucosal pattern from the axial direction of the bulb to the rather transverse direction of the second (i e , postbulbar) portion These landmarks are usually easy to recognize, but when the bulb is badly deformed, one might argue at length as to the exact site of its apex, or juncture of the bulb with the second portion In the subsequent presentation there will be considered only those ulcers which beyond question lie distal to the cap or bulb

INCIDENCE

The subject of postbulbar ulcer is a rather peculiar one, as will be seen from certain statistical data to which brief reference will be made (Fig 70) It is surprising that the relatively high incidence of postbulbar ulcers found at autopsy does not correspond in any way with the small numbers reported by roentgen examination In Fig 70 it is noted that of 158 cases of active duodenal ulcer found at necropsy, 5 per cent were present in what should be considered a strictly postbulbar position Although in this very careful study by Portis and Jaffe[3] 5 per cent of the ulcers were found beyond the bulb or cap, necropsy studies by others indicate an incidence up to 17 per cent This variation can be attributed to difficulty in identifying the exact location of an ulcer when marked deformity of the cap is present due to scarring from previous ulceration, it may then be difficult to determine whether an ulcer is in the distal portion of what was the bulb or whether it is postbulbar

A brief review of the literature disclosed only 80 cases of postbulbar ulcer demonstrated by x ray, deemed worthy of reporting (Table 6) It is obvious to any clinician or radiologist with experience in this field that postbulbar ulcer is not so rare as the literature would indicate

DIAGNOSTIC PROBLEMS

Nevertheless, there is a striking discrepancy between the incidence at autopsy and the infrequency of radiographic recognition In seeking an explanation several factors should be considered Few clinicians or radiologists have been interested in this condition sufficiently to recognize that postbulbar ulcers tend to behave somewhat differently from those in the bulb For this reason, until very recently, radiologists commonly failed to call attention to the postbulbar location of an ulcer even when its position was obvious Similarly, if marked deformity of the cap made it difficult to decide whether an ulcer was postbulbar or not, the differentiation did not seem worth quibbling over, and the lesion was reported simply as duodenal ulcer Furthermore, postbulbar ulcers often can be recognized by x ray only when the patient is viewed in the lateral projection, the radiologist who fails to include this projection routinely in his examination, will fail to demonstrate many postbulbar ulcers

Those clinical peculiarities which have attracted our attention to this lesion have been perhaps best summarized by Farinas and Alvarez (Table 7) The

Table 7 Special Features of Postbulbar Ulcer (Farinas & Alvarez)

	BULBAR	POSTBULBAR
Age	33 yrs	44 yrs
Incidence	17	1
Bleeding	12 3/	37/

observation that bleeding occurred three times as frequently in postbulbar ulcers is striking In addition there is a tendency toward certain other complications not specifically enumerated by these authors but suggested when one reviews their case abstracts a higher incidence of penetration of the ulcer into the pancreas and a higher incidence of jaundice of the obstructive type

FEATURES OF RADIOGRAPHIC DIAGNOSIS

The x ray examinations of a series of patients will now be reviewed in an effort to emphasize certain diagnostic features which seem important

Case 1 A typical postbulbar ulcer is shown in Fig 71, *A* One sees the niche in the usual position for such ulceration directed medially, one notes the constriction adjacent to it the medial deviation of the duodenum the distortion and partial destruction of the adjacent mucosal pattern In this instance there is a suggestion of slight expansion of the duodenal loop, and the gastric antrum seems pushed upward a little more than can be accounted for by extrinsic pressure by the spine, in addition, close inspection suggests that the mucosal folds of the third portion of the duodenum lean over as if ex

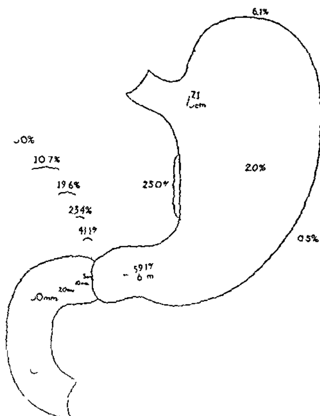


Fig 70 Topographic distribution of 196 gastric and 158 duodenal ulcers (Portis and Jaffe J A M.A 1938)

*Table 6 Reported Cases of Postbulbar Ulcers Demonstrated by X ray**

AUTHOR	DATE	NO CASES
Farinas & Alvarez	1947	16
Borman	1943	7
Sussman	1935	1
Robinson (by x ray?)	1934	10
Brule et al	1939	1
Demirleau	1939	1
Wolke	1936	12
Muochi & Martinet	1939	32†
Total		80

* Data compiled chiefly from Borman

† Out of a total of 421 cases of duodenal ulcer

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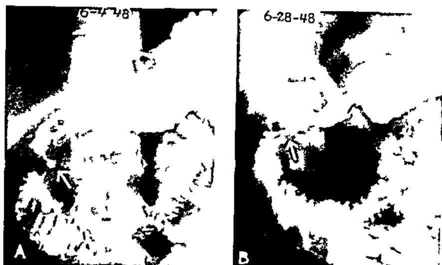


Fig 71 A typical postbulbar ulcer on June 4 1948 Crater has disappeared on reexamination June 28 1948

Fig 72 Marked distortion of postbulbar region associated with an ulcer crater (arrow) on Dec 1 1947 Review of earlier films made Dec 21 1945 shows similar deformity except that crater is absent

trinsically pressed upon These latter observations suggest that there is some swelling of the pancreas, probably inflammatory After three and one half

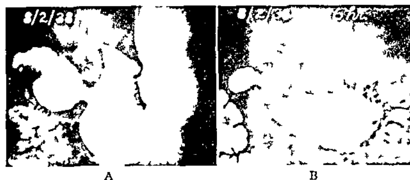


Fig 73 Postbulbar ulcer A producing considerable six hour gastric retention B

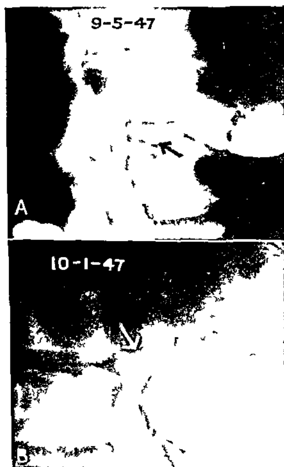


Fig 74 Postbulbar ulcer crater (A) Disappearance of crater but marked residual stenosis three and one half weeks later (B)

weeks of medical therapy, considerable improvement is noted (Fig 71, *B*) The ulcer niche has disappeared and there is greater expansion of the con stricted portion of the duodenum

Case 2 A very similar configuration is presented in this case (Fig 72, *A*) in an examination made in 1947 Fortunately there was available an older set of films of the same patient dating back to 1945 at which time the duodenum presented the appearance seen in Fig 72, *B*, showing a constriction of the proximal second portion of the duodenum which even when maximally ex panded was still quite irregular, but no ulcer niche or fleck was demonstrated It is worth noting that most postbulbar ulcer craters tend to project pos teriorly as well as medially, and when the lumen of the duodenal loop is well distended by barium the ulcer crater may be obscured

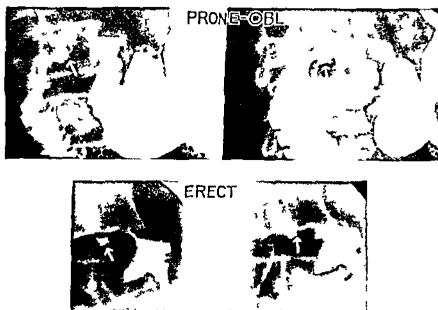


Fig 75 The importance of position in demonstrating the crater The ulcer crater in this case is identified consistently in the erect position only In some patients the recumbent position is more revealing

Case 3 (Courtesy of Dr J F Monaghan) The radiographic study was made by Dr R Bromer at Bryn Mawr Hospital in 1938 (Fig 73, *A*) Again the ulcer crater is conspicuous on the medial aspect at the juncture of the first and second portions of the duodenum Marked stenosis of the duodenum in this case produced considerable obstruction so that at the end of six hours approximately one half of the barium meal remained in the stomach (Fig 73, *B*) Sometimes a very marked degree of obstruction is noted in such cases, with the usual accompanying clinical findings

Case 4 (Courtesy of Dr J E Berk) The radiographic study of this phys ician was made by Dr G Teplick (Fig 74, *A*) The typical medial position of the ulcer crater somewhat simulates a small diverticulum except for the

inflammatory changes adjacent to it About three and one half weeks later (Fig 74, *B*) the ulcer crater has disappeared under medical management but



A



B

Fig 76 A Postbulbar ulcer with the crater directed laterally instead of mesially as usual Symptoms complicated by jaundice Ulcer crater disappeared five weeks later B and jaundice disappeared also

a marked degree of local constriction remains Attention is called to the ease with which one might overlook such a lesion at the time of either the first or

weeks of medical therapy, considerable improvement is noted (Fig 71, *B*) The ulcer niche has disappeared and there is greater expansion of the constricted portion of the duodenum

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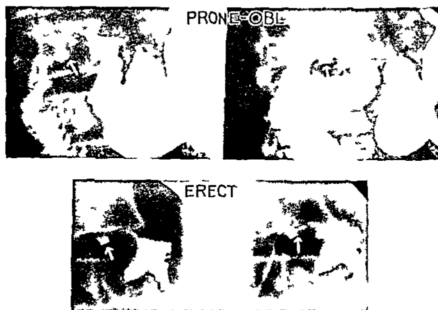


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addition to the usual symptoms of duodenal ulcer, he presented one of the not uncommon complications of a postbulbar ulcer obstructive jaundice He responded rather well to a medical regimen but his jaundice disappeared more slowly than his ulcer symptoms In his second x ray examination made about five weeks later (Fig 76, *B*) a marked improvement is indicated by disappearance of the ulcer crater and adjacent stenosis Incidentally, the patient has not been willing to adhere to a strict medical regimen, and with recurrent bouts of ulceration has had recurrent jaundice

Case 7 (Courtesy of Dr J F Monaghan) The radiographic studies were made by Dr R Bromer at the Bryn Mawr Hospital These films are pre-

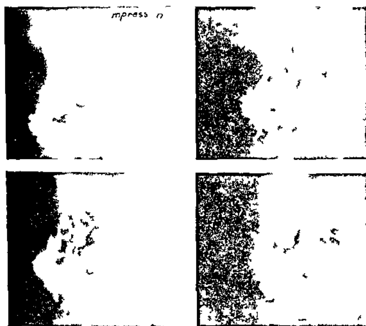


Fig 78 An unusually large postbulbar ulcer simulating a diverticulum

sented to show a peculiar radiolucence within the large postbulbar ulcer crater at the time of the first examination (Fig 77 *A*), probably due to a blood clot within the crater Three weeks later (Fig 77, *B*) the crater has decreased moderately, and twelve days later has almost completely disappeared (Fig 77, *C*) but a marked degree of residual stenosis has persisted One can only surmise that this patient may be apt to develop obstruction in the future

Case 8 Here is another postbulbar ulcer which is typical with the exception that the crater is unusually large (Fig 78) In certain respects it might be mistaken for a diverticulum and it is for the latter reason that it is being shown It should be compared with the ordinary diverticulum in this portion of the duodenum which the next case presents (Fig 79)

second examination If sharply rotated or lateral views of the duodenum are not employed routinely, one will overlook many of these craters and may completely fail to make the diagnosis of an ulcer in this location Or, if the ulcer crater is only partially visualized superimposed on the outlines of a deformed bulb, it may be misinterpreted as a pseudodiverticulum This aspect of the radiographic technic is quite important

Case 5 The radiographic study of this patient (Fig 75) is presented in order to emphasize the importance of a complete x-ray examination including films exposed in both the erect and recumbent positions, if diagnostic accu

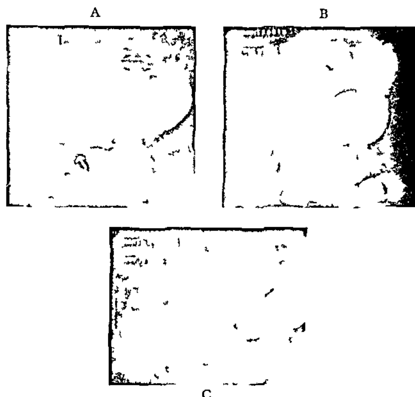


Fig 77 A large postbulbar ulcer shows a peculiar central radiolucence possibly due to a blood clot Rapid healing occurred leaving marked residual stenosis

racy is to be achieved In this case a deformity of the bulb and a pseudodiverticulum of the greater recessus are well seen in both the erect and recumbent positions However, the presence of a postbulbar ulcer crater is demonstrated definitely only in the erect position In some patients the recumbent exposures have been more revealing The most accurate results are obtained by employing both erect and recumbent views

Case 6 (Courtesy of Dr G Perakos) The roentgen findings in this case are not unusual except that the ulcer crater is directed to the right of the duodenal loop (Fig 76) The persistent narrowing of the adjacent duodenal loop is striking From the clinical standpoint this patient was interesting because in

DIFFERENTIAL DIAGNOSIS

Case 9 The most common condition to be differentiated from a postbulbar ulcer is the *duodenal diverticulum* This is usually quite simple Diverticula usually arise at a lower level, in the para-ampullary region They are frequently multiple (in about 40 per cent of the cases), and they are usually variable in size during different phases of duodenal peristalsis As one sees in Fig 79, they commonly present a mucosal pattern in the neck or stalk tend to be more bulbous and smoothly outlined at the end Above all in the vast majority of instances the diverticula do not show evidence of inflammatory involvement of the adjacent duodenal loop, that is, there is no organic nar-

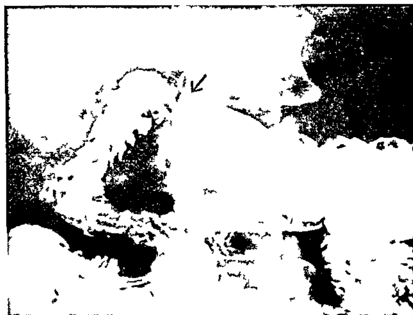


Fig 81 Short constriction of duodenal cap near its apex due to periduodenal adhesions (verified) Compression films (not illustrated) show smooth convergence of mucosal folds without distortion

rowing local spasm, mucosal distortion or local displacement of the loop by the traction of adhesions

Case 10 Uncommonly *barium in the ampulla* may present a configuration somewhat simulating a postbulbar ulcer Barium in the ampulla is usually present in such a transitory fashion that one can barely see it In Fig 80, *A*, a linear streak of barium is seen in the ampulla along the medial aspect of the mid-descending portion of the duodenal loop, whereas in Fig 80 *B* which represents an exposure made a few minutes later there is only a trace of barium in the same site Other exposures, not reproduced here, demonstrate good filling of the duodenal loop without evidence of local inflammation Incidentally, attention is called to the deformed duodenal cap, in the distal third



Fig 79 Diverticulum of proximal duodenal loop showing change in size lack of deformity of adjacent duodenum and absence of mucosal distortion thus differing from an ulcer crater

A





B

Fig 80 Barium in ampulla A usually leaves promptly B There is no local deformity of adjacent duodenum

operative periduodenal adhesions Since the patient has not been subjected to a second operation, there has been no opportunity to verify or disprove this roentgen interpretation



Fig 83 Narrowing and mucosal distortion suggesting postbulbar ulcer in a man aged thirty seven At operation it was found due to carcinoma of the head of the pancreas invading the duodenum

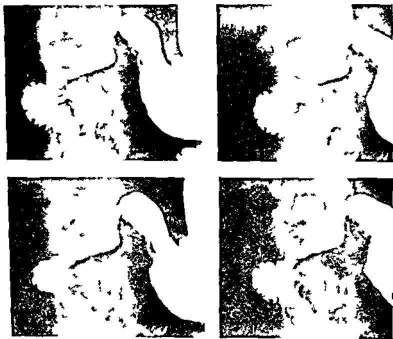


Fig 84 Constriction displacement and intact mucosal pattern indicate extrinsic pressure not a postbulbar ulcer Extrinsic pressure by carcinoma of the pancreas verified

Case 13 This thirty seven year old man presented considerable upper gastrointestinal bleeding and intractable pain On the basis of his roentgen

of which an ulcer crater is identified *For the reasons mentioned above,* barium in the ampulla is not apt to be mistaken for a postbulbar ulcer

Case 11 A constant constriction at the *apex of the bulb is demonstrated in* many exposures, of which Fig 81 is a typical example Compression expo sures (not reproduced here) show *smooth convergence of the mucosal folds* without distortion at the site of the constriction The radiologic diagnosis was *periduodenal adhesions, this was verified on subsequent operation Thus a* third type of lesion which may simulate postbulbar ulcer or ulcer scar is the periduodenal adhesion arising from one cause or another

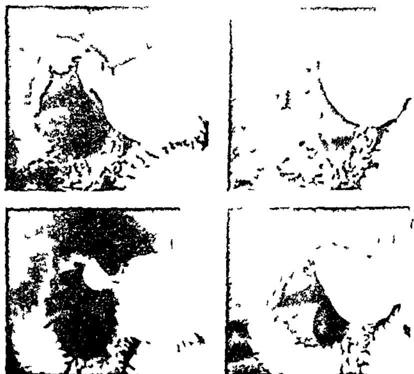


Fig 82 Long constriction without mucosal distortion in proximal second portion of duodenum Probably due to adhesions from previous cholecystectomy (unverified)

Case 12 When a longer area of constriction is encountered in the second portion of the duodenum and when this region is slightly displaced as in Fig 82, it may not be possible to determine by x-ray examination whether the configuration is due to periduodenal adhesions or whether it is due to scarring from a previous postbulbar ulcer *If the mucosal pattern is adequately visual ized and is not distorted,* it is fairly certain that a previous postbulbar ulcer was not the cause When the status of the mucosal pattern is somewhat in doubt as in the present case the interpretation may be strongly influenced by the patient s symptoms and *previous history In the present case, the patient* gave a history of previous cholecystectomy When all factors are considered it would seem most likely *that the configuration of the loop is due to post-*

nature of this deformity was not recognized preoperatively At operation the patient presented a typical segment of nonspecific enteritis elsewhere in the small intestine The first and second portions of the duodenum at operation presented a very similar configuration which is believed also to be due to *nonspecific regional enteritis* This rare lesion is included merely to indicate the wide range of diagnostic possibilities which must be kept in mind in the differential diagnosis of postbulbar ulcers

Rare in this geographic location but probably of importance elsewhere is the occurrence of deformities of the first and second portions of the duodenum due to *hookworm infestation* as reported by Yenikomshian and Shehadi [4] and others

In conclusion, attention has been drawn to a peculiar condition which almost all of us have seen, but to which few of us have paid much attention When our interest has been aroused by the realization that postbulbar ulcers occur much more frequently than had been suspected, and are probably associated with a higher incidence of certain complications especially bleeding, there is little doubt that these lesions will be recognized with much greater frequency in the future

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THE NUTRITIONAL STATUS OF THE PATIENT WITH PEPTIC ULCER

JOHN H WILLARD, M D

There appear to be two major questions involved in the problem of nutrition in peptic ulcer first is malnutrition of any proved etiologic importance in peptic ulcer and secondly, what part do nutritional factors play in the course of peptic ulcer?

MALNUTRITION IN THE ETIOLOGY OF PEPTIC ULCER

About fifteen years ago several papers were published regarding the possible etiologic importance of *vitamin C deficiency* in peptic ulcer [1] This vitamin was known to be necessary for normal tissue repair and also to be closely related to various hemorrhagic disturbances Animal experiments with vitamin C-deficient diets resulted in formation of acute gastric ulcerations in guinea pigs, rats and dogs Many investigators [3] reported that patients with peptic

studies (Fig 83) a diagnosis was made of postbulbar scarring from previous ulceration Although a definite ulcer crater was not demonstrated, its presence was suggested by a small faint fleck of barium at the apex of the cap The patient was operated upon because of the intractable nature of his symptoms A carcinoma of the pancreas was found, secondarily invading the postbulbar portion of the duodenum Thrown off guard by the relative youth of this patient, preoperatively I had failed to consider the possibility of *malignancy* The *increasing frequency* with which carcinoma is being encountered in young individuals is all too slowly dispelling our complacency in considering it chiefly a disease of middle life and later years

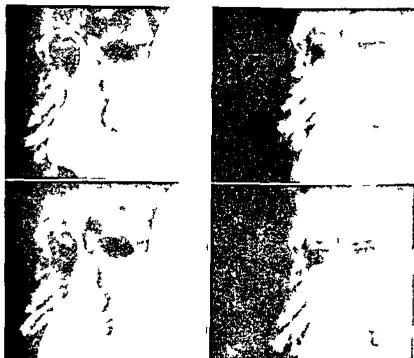


Fig 85 A rare instance of regional nonspecific enteritis producing stenosis of apex of cap and postbulbar area

Case 14 The constriction of the distal portion of the bulb (Fig 84) and the postbulbar region, their slight displacement, and the fairly intact mucosa—all point to *extrinsic pressure* as the cause of this deformity The associated con cavity of the greater curvature aspect of the gastric antrum suggests that the extrinsic pressure is a pancreatic tumor A pancreatic carcinoma was found at operation There is little doubt, as illustrated by Cases 13 and 14, that car cinoma of the *pancreas is the most important and most difficult* condition to be differentiated from a benign postbulbar ulcer *Primary malignancy* of the duodenum is so rare that it does not present an important problem

Case 15 The peculiar narrowing of the apex of the duodenal bulb and the proximal second portion *of the duodenum is illustrated in* Fig 85 The

nature of this deformity was not recognized preoperatively At operation the patient presented a typical segment of nonspecific enteritis elsewhere in the small intestine The first and second portions of the duodenum at operation presented a very similar configuration which is believed also to be due to *nonspecific regional enteritis* This rare lesion is included merely to indicate the wide range of diagnostic possibilities which must be kept in mind in the differential diagnosis of postbulbar ulcers

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ulcer usually had deficient intake of vitamin C and many showed low blood levels This was particularly true in those who showed a tendency to bleed from their ulcers In spite of these suggestive findings, there are no data to indicate that vitamin C deficiency is of definite etiologic importance in human peptic ulcer disease [4]

The possibility of *vitamin B deficiency* being of etiologic importance also has been investigated, especially since patients with digestive symptoms frequently lower their intake of B complex-containing foods, and since large doses of alkalis are known to destroy thiamine While such deficiencies occasionally may appear in ulcer patients, there is nothing to indicate that deficiency of any of the B complex factors may produce peptic ulcer in man [4]

More recently, attention has been directed toward the possible relationship between *protein and amino acid deficiencies* and peptic ulcer Interest was stimulated by the reports of Co Tui[5] and others that many ulcer patients were benefited by high protein intake The possible etiologic importance of amino acid deficiencies was suggested by Weiss and Aron in 1933 [6] These workers postulated that deficiency of certain amino acids decreased tissue resistance to the digestive effect of hydrochloric acid and pepsin Hoelzel and Da Costa in 1937[7] produced gastric ulcerations in rats and mice kept on protein or amino acid-deficient diets Later Matzner and his associates[8] reported that 85 per cent of the rats kept on a basic low protein diet developed gastric ulcerations when given hydrochloric acid pepsin preparations Animals given a high protein diet developed ulcers in only 10 per cent

Here again, in spite of these very suggestive observations, there are no data indicating that protein or amino acid deficiency is a cause of peptic ulcer in man *It would appear, therefore, that to date there is no proof of the etiologic* relationship between vitamin or protein deficiency and human peptic ulcer

MALNUTRITION DURING THE COURSE OF PEPTIC ULCER

The beneficial effect of adequate protein nutrition on the clinical course of peptic ulcer has been emphasized by the work of Co Tui and others [5] One wonders how often malnutrition is an important factor in these patients Most physicians are not impressed by the frequency of clinical evidences of *deficiencies in the usual uncomplicated ulcer patient seen in office or clinic* Those patients with complications such as pyloric obstruction or hemorrhage, on the other hand, often show signs of nutritional disturbances

In spite of the lack of evidence of deficiencies in the average ulcer patient, there are numerous data in the literature suggesting frequent *potential deficiencies* Boles and his collaborators[3] in 1941 studied 52 ulcer patients at the Philadelphia General Hospital and found that the mean average of serum proteins was lower than in a control group, in 17 of this group the serum protein levels were definitely below normal Later, the same workers analyzed the diets of a similar group of *ulcer patients and found that 19 per cent* were below minimal requirements for protein, 44 per cent below minimal requirements for fat and 29 per cent were below minimal requirements for vitamin C, 78 per cent below minimal requirements for vitamin B, and 30 per cent below

minimal requirements for calcium and iron Spies in 1943 reported that the usual Sippy schedule provided only 17 per cent of the vitamin C requirements, 40 per cent of the thiamine, 60 per cent of the riboflavin and 20 per cent of the nicotinic acid requirements

The possible clinical importance of subclinical protein deficiency states is suggested by two pieces of work which I believe to be of great significance In 1933, Chester Jones and his collaborator, Eaton,[10] commented on the fact that many patients operated upon for peptic ulcer developed, in the post operative phase, definite evidence of protein deficiency peripheral edema, pulmonary edema and the other complications They pointed out a very important fact that in none of these individuals was there preoperative clinical evidence of deficiency, yet in those who had been on a strict diet for some time or who had been vomiting evidence of protein deficiency appeared as soon as ample salt and water was administered It was also suggested that the use of alkalis under these conditions was likely to precipitate evidence of hypo proteinemia indicated by water retention

Further significant work was reported by Ravdin et al [11] in 1937 Dogs, made hypoproteinemic by deficient diets plus plasmapheresis showed definite delay in gastric emptying in 6 of 8 cases This delay was roughly proportional to the degree of hypoproteinemia but was not due to gastric atony since most of the dogs showed gastric hypertonicity and hyperperistalsis Similarly, dogs with gastric operations were found to show delayed motility and in some resected animals there were late complications such as duodenal stump perforation and rupture of jejunal ulcerations

These reports suggest that, while in most patients with uncomplicated peptic ulcers there is no clinical deficiency, potential hypoproteinemia and hypovitaminosis may be present and may be of importance in the development of complications such as obstruction and hemorrhage Certainly the likelihood of postoperative complications is much greater in malnourished individuals

In patients with complications such as pyloric obstruction or hemorrhage, the incidence of deficiencies is much higher than in the uncomplicated group of ulcer patients Sappington,[12] at the Graduate Hospital, in studying nitrogen balance found that practically every complicated ulcer patient was in a state of negative balance, and Kennimore[13] reported that each of a series of ulcer patients kept on the usual ulcer regimen remained in negative nitrogen balance until given a higher protein intake These observations substantiate the clinical findings of Co Tui and others that many ulcer patients respond better to programs including a high protein intake

It would appear therefore that while there is little if any, evidence that vitamin or protein deficiencies are of etiologic importance in peptic ulcer disease potential deficiencies may be more common than is generally appreciated and may be of some significance in the pathogenesis of complications of peptic ulcer Furthermore there is good evidence that any patient who has been vomiting or who has pyloric obstruction or who has recently bled is at least potentially deficient and may be thrown into definite deficiency by operation and/or fluid and salt administration Certainly in these patients every effort

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in ulcer requires information regarding its effects on duodenal bulb as well as gastric acidity I hold to this opinion because most clinical ulcers are situated in the duodenal bulb and not in the stomach and the mechanisms at play are not entirely similar

For these reasons, Dr Lopusniak and I undertook to study the effects of a preparation of casein hydrolysate on gastric and duodenal bulb acidity in a specially selected group of patients with active duodenal ulcer At the same time we sought to compare these effects with those of milk or mixtures of milk and cream when fed to the same subjects under similar circumstances I should like to underscore the point that with respect to the latter goal we were interested primarily in comparing *clinical* methods of treating ulcer, it was not our intention to compare the effects on acidity of equivalent amounts

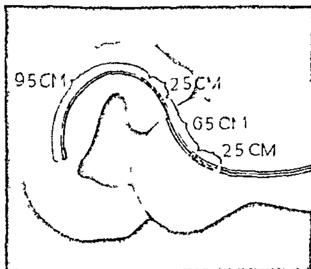


Fig 86 Relative positions and distances between tip, markers and perforations of gastroduodenal tube (Berk J E Rehfuss M E and Thomas J E in J.A M A Vol 119)

and iso-osmotic concentrations of native whole protein and hydrolyzed protein Therefore, we elected to use the dosage and frequency of administration of casein hydrolysate recommended for general use in ulcer management at the time our studies were begun As described by the pharmaceutical concern manufacturing the particular preparation, this called for an aqueous suspension of 30 gm each of casein hydrolysate and a special carbohydrate given every other hour For purposes of comparison we used hourly feedings of whole milk or a mixture of 5 parts of milk and 1 part of cream since these constitute the cornerstone of the dietary management of active duodenal ulcer employed by our colleagues and us

MATERIAL

Eleven patients were selected who were under treatment on the service of Dr Bockus at the Graduate Hospital for symptomatic but uncomplicated

should be made to establish positive nitrogen balance by administration of adequate vitamins and proteins, orally, if possible, or intravenously, if necessary This is particularly indicated if surgery is contemplated

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THE BUFFERING CAPACITY OF PROTEIN HYDROLYSATES AND OTHER FEEDINGS UTILIZED IN THE TREATMENT OF PEPTIC ULCER PRACTICAL APPLICATION

J EDWARD BERK, M D

Hydrolyzed protein has been advocated in recent years in the treatment of gastroduodenal ulcer This is a reflection in large part of the growing recognition of the importance of protein in health and disease It has been claimed that hydrolyzed protein is of value in ulcer disease not only because it is a potent source of amino nitrogen for body metabolism, but also because it possesses antacid properties However, the observations reported in the literature to date on the in vivo buffering capacity of hydrolyzed protein have without exception been confined to the stomach The methods of study have varied and the conclusions drawn have by no means been in agreement Furthermore, the subjects selected for study have not all been individuals with chronic gastric or duodenal ulcer

It has always seemed to me of utmost importance in the evaluation of any substance advocated for treating ulcer, to determine its effects when administered to patients with an active gastric or duodenal ulcer I also believe that proper evaluation of the antacid properties of any substance intended for use

in ulcer requires information regarding its effects on duodenal bulb as well as gastric acidity I hold to this opinion because most clinical ulcers are situated in the duodenal bulb and not in the stomach, and the mechanisms at play are not entirely similar

For these reasons, Dr Lopusniak and I undertook to study the effects of a preparation of casein hydrolysate on gastric and duodenal bulb acidity in a specially selected group of patients with active duodenal ulcer At the same time we sought to compare these effects with those of milk or mixtures of milk and cream when fed to the same subjects under similar circumstances I should like to underscore the point that with respect to the latter goal we were interested primarily in comparing *clinical* methods of treating ulcer, it was not our intention to compare the effects on acidity of equivalent amounts

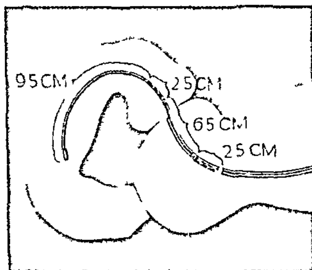


Fig 86 Relative positions and distances between tip markers and perforations of gastroduodenal tube (Berk J E Rehfuss M E and Thomas J E in J A M A Vol 119)

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MATERIAL

Eleven patients were selected who were under treatment on the service of Dr Bockus at the Graduate Hospital for symptomatic but uncomplicated

duodenal ulcer Some were studied while in the hospital while the rest were observed in the Gastro-Intestinal Clinic All had symptoms indicative of active recurrent ulcer at the time or up until a few days before studies were performed In 7 of the 11, an ulcer niche was demonstrated in the duodenal bulb just before the tests were initiated



Fig 87 Duodenal ulcer A film taken in erect position at the time of barium sulfate meal study showing deformed duodenal cap with pseudodiverticulum formation B film taken at time of gastroduodenal analysis showing position of tube Note position of tip markers and perforations C film taken after injection of barium sulfate through the duodenal portion of the tube Arrow indicates relationship of proximal duodenal marker to base of cap (Berk J E Rehfuss M E and Thomas J E in J A M A Vol 119)

METHOD

Each patient was studied in the morning after a fast of approximately twelve hours A specially constructed double-lumen tube was introduced into the duodenum under *fluoroscopic control This tube was so arranged as to permit* simultaneous extraction of material from either side of the pylorus (Fig 86) Throughout the entire period of observation the subject remained on a hori-

zontal fluoroscopic table The location of the tube in the desired position was verified fluoroscopically before each extraction A roentgenogram was taken immediately before the administration of the foodstuffs so as to have a record of the position of the tube At the completion of each study other roentgenograms were taken, before and immediately after the administration of barium through the duodenal limb so as to outline the duodenal bulb and afford proof that the duodenal openings were correctly situated within it (Fig 87)

Specimens were simultaneously withdrawn from the pyloric antrum and duodenal bulb by the use of a suction apparatus employing an electric pump and a negative pressure varying from 25 to 40 mm of mercury Samples were collected under fasting conditions at ten minute intervals for from twenty to thirty minutes or until a more or less basal secretory state had been reached Following this the material under investigation was ingested and fractional samples were simultaneously removed from the stomach and duodenum at ten minute intervals for a total of two hours Each test substance was studied on different days so that observations during any one morning were confined to a single substance

The hydrolyzed protein mixture, hereafter referred to as PDM, contained 30 gm of casein hydrolysate (Protolysate) and 30 gm of a mixture of dextrins and maltose (Dextri-Maltose No 2) suspended in 90 cc of water for a total of 120 cc of suspension This was administered in the fasting state only and was not repeated during the two hour observation period The milk used was whole homogenized cow s milk This was administered in the fasting state and again after one hour The milk cream mixture consisted of 5 parts of whole homogenized cow s milk and 1 part of ordinary table cream (approximately 20 per cent fat) This likewise was administered in the fasting state and again after one hour

The pH of each gastric and duodenal sample was determined immediately after extraction and before filtration Following filtration the free and total acidity of each specimen was titrimetrically determined using Topfer s reagent and phenolphthalein as the respective color indicators

RESULTS

GASTRIC ACIDITY

It is apparent from the plotted curves of mean gastric pH shown in Fig 88 that there was less effective gastric acidity after PDM than after milk cream or milk It is likewise apparent, however, that despite this hydrolyzed protein resulted in a not inconsiderable degree of gastric acid secretion and left much to be desired as a buffer and neutralizer of gastric acidity In one patient the gastric pH after PDM was never elevated above 3 5 This pH value was chosen as the critical value for neutralization of free acid because it corresponds to 1 mN of free HCl and therefore virtually represents complete neutralization of the substance Judged on this basis, the maximum duration of neutralization of gastric free acid following PDM in these ulcer patients was ninety minutes and this occurred in only one individual Moreover, this same

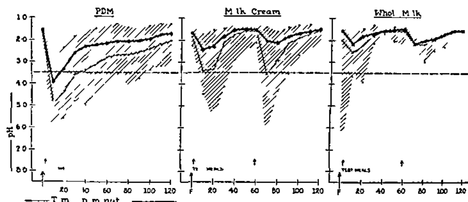


Fig 88 The mean maximum and minimum pH of the contents of the pars pylorica before and over a period of two hours after (1) a single feeding of protolysate–dextri maltose (PDM) (2) two feedings of milk cream an hour apart and (3) two feedings of milk an hour apart The heavier graphic line represents the arithmetic mean computed by transposing each pH reading at each time interval to its corresponding hydrogen ion concentration and then simply averaging the latter and expressing the resultant mean in terms of pH The lighter graphic line represents the arithmetic mean calculated by simply averaging the actual pH values at each time interval. (Lopusniak M S and Berk J E in Gastroenterology Vol 11, published by Williams & Wilkins Company Baltimore Maryland)

PDM
MILK CREAM (5 1)
WHOLE MILK
pH

Fig 89 The distribution of the pH values of the contents of the pars pylorica obtained at ten minute intervals over a two hour period after (1) a single feeding of protolysate–dextri maltose (PDM) (2) two feedings of milk cream an hour apart and (3) two feedings of milk an hour apart (Lopusniak M S and Berk J E in Gastroenterology, Vol 11, published by Williams & Wilkins Company Baltimore, Maryland)

subject when studied on a later occasion showed persistent neutralization of free acid in his gastric contents for only forty minutes Even the most favorable graphic figure, that representing the mean pH arrived at by averaging the pH values, shows that the mean pH of the gastric contents following PDM remained above the critical value of 3 5 for only thirty minutes

The distribution of the pH values of the contents of the pars pylorica following milk and milk-cream showed a clustering on the low side of the pH scale (Fig 89) None of the samples obtained from the stomachs of these patients after both feedings of milk had a pH in excess of 4 0 A few of the samples secured after milk-cream exceeded pH 4 0, but in 71 per cent the pH was less than 2 5 In contrast, the samples after PDM showed a much

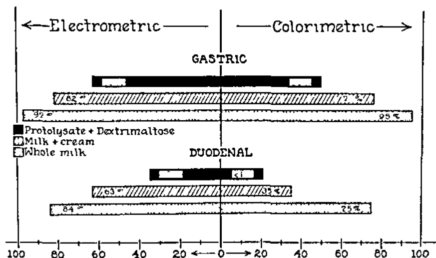


Fig 90 The percentage of gastric and duodenal samples positive for free acid over a period of two hours after (1) a single feeding of protolysate–dextri maltose (2) two feedings of milk cream an hour apart and (3) two feedings of milk an hour apart. On the right are the comparative percentages determined by the use of Topfer s reagent (colorimetric) On the left are the comparative percentages determined from the actual pH values (electrometric) Those samples which had a pH of less than 3 5 were considered positive for free acid (Lopusniak M S and Berk J E in Gastroenterology Vol 11 published by Williams & Wilkins Company Baltimore Maryland)

wider range of distribution with 56 per cent falling between pH 2 5 and pH 4 5 Figure 89 also clearly shows that the percentage of gastric samples positive for free acid (i e samples with a pH less than 3 5) was definitely less after PDM than after milk-cream or milk

An interesting observation had to do with the discrepancy between the percentage of samples considered positive for free acid as determined by ordinary clinical titration employing Topfer s reagent as the color indicator, and the percentage whose electrometrically determined pH was within the free acid range (less than 3 5) (Fig 90) As may be seen in Fig 90 the percentage of samples colorimetrically positive for free acid was less for each of the three foodstuffs than the percentage electrometrically positive This means that

many times free acid may be erroneously interpreted as absent when the test is performed in the ordinary way using a color indicator By the same token, antacid properties greater than warranted may be ascribed to these or other

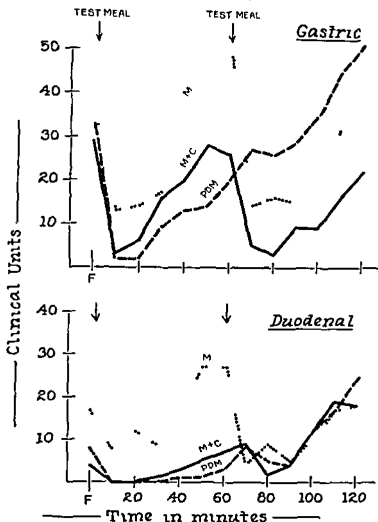


Fig 91 The mean titrimetric free acidity of the contents of the pars pylorica and first part of the duodenum, before and over a period of two hours after (1) a single feeding of protolysate–dextri maltose (PDM) (2) two feedings of milk-cream an hour apart, and (3) two feedings of milk an hour apart The values from which these graphs were constructed were obtained by titrating the respective samples with sodium hydroxide using Topfer s reagent as the color indicator (Lopusniak M S and Berk J E in Gastroenterology Vol 11, published by Williams & Wilkins Company Baltimore, Maryland)

test substances if observations are restricted to measurements relying on color indicators

Titrimetric determination of free acid in the gastric contents showed a progressive and steady rise in free acid beginning twenty minutes after ingestion of PDM (Fig 91) This rise was most pronounced in the interval from ninety

to one hundred and twenty minutes after feeding even though the mean gastric pH during the same period showed little change (Fig 88) Similar secondary stimulation of gastric free acid secretion appeared to follow milk and milk-cream (Fig 91) However a rigid comparison cannot be made be tween these preparations and hydrolyzed casein because they were each fed twice while the PDM was administered only once during the two-hour observation period

DUODENAL BULB ACIDITY

In the first part of the duodenum, just as in the distal stomach, the effective acidity was less after PDM than after milk-cream or whole milk (Fig 92) Nevertheless, pH values well within the free acid range were obtained at all

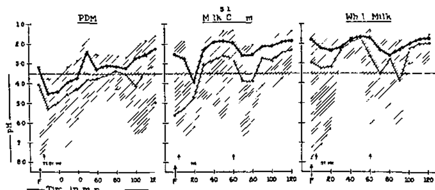


Fig 92 The mean maximum and minimum pH of the contents of the duodenal bulb before and over a period of two hours after (1) a single feeding of protolysate-dextri maltose (PDM) (2) two feedings of milk cream an hour apart and (3) two feedings of milk an hour apart The heavier graphic line represents the arithmetic mean computed by transposing each pH reading at each time interval to its cor responding hydrogen ion concentration and then simply averaging the latter and expressing the resultant mean in terms of pH The lighter graphic line represents the arithmetic mean calculated by simply averaging the actual pH values at each time interval (Lopusniak M S and Berk J E in Gastroenterology Vol 11 published by Williams & Wilkins Company Baltimore Maryland)

intervals except during the first twenty minutes following the ingestion of the hydrolyzed protein mixture Also, the mean pH, computed from the pH readings themselves, consistently remained above the critical level for free acid (3 5) for only seventy minutes Furthermore, despite the generally higher mean duodenal pH after PDM the difference in the means at each post-prandial interval following this preparation as compared with those following milk-cream was statistically significant only at thirty and forty minutes, at seventy and eighty minutes the advantage actually lay with milk-cream In 6 patients on whom observations were made after both substances the difference in the means of duodenal pH was without statistical significance at each of the postprandial intervals This finding appeared to be especially note worthy since in these same patients the difference in mean gastric pH after PDM and milk-cream was statistically significant

many times free acid may be erroneously interpreted as absent when the test is performed in the ordinary way using a color indicator By the same token, antacid properties greater than warranted may be ascribed to these or other

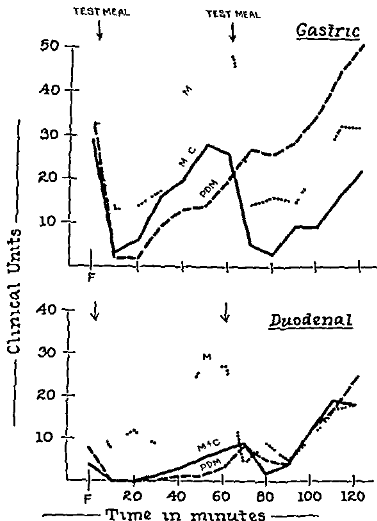


Fig 91 The mean titrimetric free acidity of the contents of the pars pylorica and first part of the duodenum before and over a period of two hours after (1) a single feeding of protolysate–dextri maltose (PDM) (2) two feeding of milk cream an hour apart and (3) two feedings of milk an hour apart The values from which these graphs were constructed were obtained by titrating the respective samples with sodium hydroxide using Topfer s reagent as the color indicator (Lopusniak, M S and Berk J E in Gastroenterology Vol 11 published by Williams & Wilkins Company, Baltimore Maryland)

test substances if observations are restricted to measurements relying on color indicators

Titrimetric determination of free acid in the gastric contents showed a progressive and steady rise in free acid beginning twenty minutes after ingestion of PDM (Fig 91) This rise was most pronounced in the interval from ninety

free acidity was demonstrated following PDM (Fig 91) This rise in mean duodenal free acid was most pronounced during the final hour of the post-cibal period A similar rise in duodenal free acid followed milk-cream and milk, but no valid comparisons can be made with that after casein hydrolysate because of differences in frequency of administration and total volume of material administered

COMMENT

The demonstrated superiority of casein hydrolysate over milk and milk-cream as a buffer and neutralizer of acid is not surprising When buffering capacity is measured in terms of the quantity of hydrochloric acid required to bring about a change in pH in mixtures containing equivalent amounts of

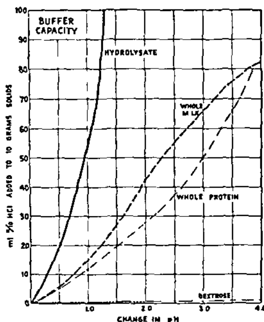


Fig 94 Comparative in vitro buffering capacity of hydrolyzed and whole protein

whole protein and hydrolyzed protein, the superior buffer capacity possessed by hydrolyzed protein is clearly evident (Fig 94)

Nor is it surprising to find that milk and milk-cream mixtures are without notable effect in reducing gastric and duodenal bulb acidity, especially in patients with active duodenal ulcer The popularity of milk as a basic constituent of the ulcer dietary appears to rest principally on its demonstrated ability to neutralize considerable volumes of relatively weak hydrochloric acid in vitro However, Rehfuss and his associates in their early studies on the combining value of various foods for hydrochloric acid, noted that when milk was fed to humans there was a perceptible rise in acidity They reported an appreciable secretion following the ingestion of milk preparations and stated that in duodenal ulcer with its hypersecretory tendency a large amount of

The distribution of pH values was much wider in the duodenal bulb than in the pars pylorica after all three foodstuffs (Fig 93) Most of the pH readings following PDM tended to cluster around higher levels than was true for milk-cream and especially for milk Here again, however, it is obvious that the buffering action of casein hydrolysate in the duodenal bulb of these ulcer patients, in spite of its apparent advantages over milk and milk cream, was not perfect Although the mean duodenal pH computed by averaging the individual pH values remained above the free acid level (3 5) for seventy minutes, neutralization of free acid in each fractional sample was maintained for only twenty minutes in all of the 8 patients studied after this preparation More than half of the samples examined at seventy minutes after ingestion of PDM contained free acid (pH less than 3 5) Furthermore, approximately

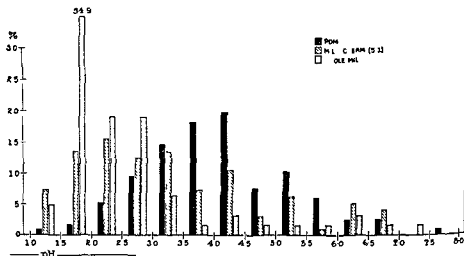


Fig 93 The distribution of the pH values of the contents of the duodenal bulb obtained at ten minute intervals over a two hour period after (1) a single feeding of protolysate-dextri maltose (PDM) (2) two feedings of milk cream an hour apart and (3) two feedings of milk an hour apart (Lopusniak M S and Berk J E in Gastroenterology Vol 11 published by Williams & Wilkins Company Baltimore Maryland)

one-third (34 5 per cent) of all the postprandial duodenal samples were positive for free acid as judged from their pH values

The discrepancy between colorimetric and electrometric methods of estimating the presence of free acid was even more marked in the duodenal bulb than in the stomach (Fig 90) This was especially true for samples obtained after PDM and milk cream The natural amber color of the former and the bile-staining of many of the latter apparently interfered with accurate interpretation of color changes on the part of the indicator The point to be stressed is that in dealing with colored solutions, free acid is apt to be mistakenly interpreted as absent when its presence or absence is determined in the usual manner with a color indicator

In the first portion of the duodenum, just as in the stomach, a late rise in

by another form of hydrolyzed protein The protein hydrolysate preparations were administered twice a day through a stomach tube in amounts equivalent to 25 per cent of additional protein The experimental feeding period lasted twenty eight days At the end of this time the rats were subjected to pyloric ligation and then sacrificed after six hours The number of rumenal ulcers developing in the *protein hydrolysate treated* groups was *significantly less* than in the control group

How then are we to reconcile the imperfect antacid action of milk, milk cream, and even hydrolyzed protein in patients with active duodenal ulcer with their beneficial clinical effects as well as with their ability to protect animals against experimentally induced ulcers? It may be that the beneficial effects obtained clinically from the use of these substances are due to something more than their ability to reduce gastric and duodenal bulb acidity In support of this possibility are additional observations made by the Fels Institute workers in the rats protected by protein hydrolysates against ulcers induced by pyloric ligation It was noted in these animals that despite the marked increase in resistance of the gastric rumen to ulceration, there was no concurrent change in volume, acidity or peptic power of the gastric contents This would suggest that the protective action of the hydrolyzed protein had more to do with increasing resistance on the part of the mucosa than with diminishing gastric secretion per se

Another explanation for the apparent disparity between the antacid properties and the clinical efficacy of these substances is the possibility that their neutralizing capacity is greater than indicated by the standards we employ to measure this capacity In considering the acid problem in ulcer we have grown accustomed to thinking in terms of free acid This we arbitrarily consider as the titratable acidity existent below pH 3 5 The generally accepted standard for effective reduction of acidity in the stomach or duodenum is neutralization of free acid or maintenance of pH above the critical level of 3 5 Hollander suggested that a more reasonable critical level would be pH 5 0 since at this point peptic activity no longer exists Still another criterion attracts us, however, especially with respect to the ulcer bearing duodenal bulb Dr Thomas and his associates have demonstrated that various autoregulatory mechanisms are activated when the acidity of the duodenal contents reaches certain critical levels These mechanisms are intended to help defend the duodenal mucosa against possible harm Thus, at pH 4 0 or below pancreatic secretion is stimulated in dogs at pH 2 5 gastric motility and gastric secretion are markedly depressed in these animals, and at pH 2 0 or below almost completely inhibited It may be more in keeping with physiologic activity therefore to consider the acidity of the duodenal contents as critical only when a level is reached which significantly influences gastric motility and secretion

CONCLUSIONS

1 In a selected group of patients with active duodenal ulcer a single feeding of 120 cc of an aqueous mixture containing 30 gm of casein *hydrolysate more*

free acid often followed milk ingestion Subsequent investigators have confirmed the fact that milk is without notable effect in reducing gastric acidity Kirsner and Palmer, for example, observed the pH of the gastric contents at hourly intervals following (a) an ordinary diet, (b) hourly feedings of 90 cc. of a mixture of milk and 7 per cent casec, and (c) hourly feedings of 90 cc of a mixture of milk and cream Milk and cream did not result in any significant elevation of pH and even the addition of 7 per cent casec to milk failed to raise the pH of the gastric contents appreciably

Despite the apparent superiority of casein hydrolysate over milk and milk cream as a buffer and neutralizer in patients with active duodenal ulcer, its antacid action is still imperfect If larger doses of the hydrolyzed casein were used, or if the material were administered hourly rather than every other hour, perhaps its antacid action would be improved However, Woldman and his associates have recently demonstrated that the hourly administration of 25 gm of hydrolyzed protein, a dose approximating the one used by us, eventually ceased to neutralize free acid in the stomach Furthermore, a secondary rise in gastric free acid secretion following casein hydrolysate was clearly demonstrated in our experiments Increasing the size of the dose might result in an even larger late rise in acidity, especially during the long interdigestive phase following the last feeding at night Finally, it is unlikely that many patients would tolerate such a distasteful mixture for any length of time if required to take large doses every hour

Our findings with respect to hydrolyzed protein are at variance with those of other investigators who observed more favorable effects on gastric acidity Their methods of study, however, differed somewhat from our own and they did not confine their observations to patients with active duodenal ulcer It is of interest, too, that those with the most favorable results determined the presence or absence of free acid solely by colorimetric means employing Topfer s reagent as the indicator Our experience would suggest that this method is not entirely reliable, particularly when titrating colored mixtures such as protein hydrolysate, free acid may appear to be absent when the actual pH of the material is well within the free acid range

The value of hourly feedings of milk or mixtures of milk and cream in the treatment of ulcer has been established by clinical observations and by long experience on the part of many clinicians More recently, animal experimentation has produced evidence supporting the helpful action of these food stuffs Fast, Friesen and Wangensteen have shown that dogs maintained on alternate feedings of whole milk and alkali were significantly protected against histamine provoked ulcer

Sufficient evidence is now at hand to indicate that hydrolyzed protein likewise is of clinical benefit in the management of patients with gastroduodenal ulcer Here, too, animal experimentation has recently afforded corroborative evidence Shay, Gruenstein, Siplet and Komarov, working at the Fels Research Institute of Temple University School of Medicine, fed each of three groups of rats a standard Rockland diet This basic and adequate diet was supplemented in one group by one form of hydrolyzed protein and in another group

absorbed from the intestine but to a specific inhibitory hormone liberated from the intestine

In 1928 Walawski reported that the Ringer Locke solution in which blood-free intestine had been soaked inhibited gastric secretion provoked by histamine, and in 1930 Kosaka and Lim reported also that saline extracts of intestinal mucosa inhibited secretion from the denervated gastric pouch of the dog The latter workers believed the inhibitory effect to be due to a specific chalone (or inhibitory hormone) which they designated ' enterogastrone In addition to depressing gastric secretion, the intestinal extracts were also found to depress gastric hunger contractions and gastric motility initiated by gastric distention or insulin hypoglycemia Ivy and his coworkers subsequently improved the extraction procedures for preparation of enterogastrone concentrates and to them we owe much of our present knowledge of its properties and effects It is still unsettled whether the inhibition of secretory and motor functions is due to a single chalone or whether two enterogastrones are involved (Lim 1933), the more recent work of Ivy and collaborators would favor the view of two more or less distinct principles with specific inhibitory actions

The presence of a substance in human urine with a depressant action on gastric secretion was reported independently by three groups of workers in May 1939 by Gray Wieczorowski and Ivy in June 1939 by Friedman, Recknagel Sandweiss and Patterson and in November 1939 by Necheles, Hanke and Fantl In addition to depressing gastric secretion these urine extracts were found also to depress in the dog both gastric hunger contractions and gastric motility induced by insulin hypoglycemia The substance has been found in the urine of animals as well as man However, as in the case of enterogastrone, the question whether a single factor or two distinct factors are responsible for inhibiting both the secretion and motor activities of the stomach is still unsettled

The resemblance of the urinary gastric secretory depressant to enterogastrone in physiologic effect and the belief that a high fat diet led to an augmented excretion, led Ivy and his coworkers to designate the active principle as urogastrone At the same time however, Friedman, Saltzstein and Farbman reported that the principle was still excreted in the urine of dogs after removal of either the stomach or intestine and concluded that it probably was not of enteric origin Subsequently Gray, Culmer Wells and Wieczorowski also came to the conclusion that enterogastrone and urogastrone probably were two different entities This conclusion was further strengthened by studies on the chemical properties of the two substances Neither the site nor the mechanism of elaboration of the urinary principle has been established A gastric secretory depressant was demonstrated in the urine of normal men and women pregnant women, patients with either gastric ulcer or duodenal ulcer patients with gastric carcinoma and patients with pernicious anemia (Table 8) Certain experiments of Patterson et al would seem to implicate the pituitary but their results are difficult to evaluate A diminished output of gastric secretory [illegible] dogs with induced liver damage

effectively buffered and neutralized gastric and duodenal bulb acidity over a two-hour period than did 120 cc of milk or a mixture of milk and cream (5 1) fed hourly over an equal period

2 The superiority of the casein hydrolysate mixture over milk and milk-cream as a buffer and neutralizer was quite definite in the stomach, but did not appear to be significant in the first part of the duodenum

3 Despite its apparent superiority over milk and milk-cream as an antacid, the casein hydrolysate mixture was nevertheless imperfect in its ability to buffer and neutralize gastric and duodenal bulb acidity in these duodenal ulcer patients

4 Fairly marked secondary stimulation of acid secretion in the stomach regularly followed feeding of the hydrolyzed protein mixture

5 It is suggested that (a) the clinical improvement repeatedly observed following the use of milk, milk-cream or casein hydrolysate mixtures in patients with duodenal ulcer is due to more than the reduction in gastric and duodenal bulb acidity which they bring about, or (b) the effectiveness of these substances in reducing gastric and duodenal bulb acidity is greater than the current standards of measuring such effectiveness would indicate

ENTEROGASTRONE AND UROGASTRONE IN PEPTIC ULCER

An Experimental and Clinical Appraisal

M H F FRIEDMAN, PH D

EXPERIMENTAL STUDIES

There is abundant experimental evidence that gastric secretion and motility may be depressed by the introduction into the intestine of adequate amounts of fat, sugars or solutions of dilute acid These inhibitory effects on the gastric glands and musculature are due in part no doubt to reflexes from the intestine but also in part to a humoral mechanism The nervous mechanism for inhibition usually is masked by the humoral mechanism and therefore can be demonstrated only in special experiments

The earlier literature has been reviewed by Babkin and Ivy and Gray and need be cited here only briefly In dogs with the stomach isolated from its autonomic innervation or with an autotransplanted gastric pouch in which the extrinsic nervous connections have been severed, the introduction of fat into the duodenum inhibits gastric secretion and gastric motility, no such inhibitory effect, however, is obtained when fat glycerin, sodium oleate or thoracic duct lymph is injected intravenously Such experiments indicate that the inhibition of the denervated stomach is not due to the digestion products

Mann-Williamson ulcer using extracts of duodenal mucosa, this work too has been confirmed elsewhere

The question arises is the healing of the experimental ulcer by extracts of duodenal mucosa and of urine due to the inhibition of gastric secretion? At present all the evidence points to the negative While chemical separation has not been achieved as yet, it is becoming clear that *the factor in both intestinal extracts and urine extracts which is responsible for protecting against the experimental ulcer is distinct from the secretory depressant factor* This is an important point since it should determine the choice of the assay procedure to be used in isolating the anti ulcer factor in both intestinal extracts and urine

Among the procedures most commonly in use to test the potency of extracts to depress gastric secretion are those employing the pouch dog and the

Table 9 Treatment of Mann Williamson Dogs with Extracts of Human Urine

TREATMENT	NO DOGS	WITHOUT ULCERS	HEALING ULCERS	SURVIVED LONGER THAN 135 DAYS	AVERAGE POSTOP SURVIVAL DAYS	PERFORATIONS %	BENEFICIAL EFFECT %
Control	28	0	2	0	71	72	10
Pregnancy urine	42	19	9	12	169	20	85
Normal female urine	42	8	10	15	140	54	62
Ulcer patients urine	30	3	2	3	71	76	24

pylorus ligated rat The inhibition of secretion from the Heidenhain pouch of a dog receiving either repeated or single injections of histamine resulting from administration of the extract is a measure of the secretory depressant action of the extract The pylorus-ligated rat as an assay preparation was first demonstrated in 1940 by Friedman and Sandweiss at the Scientific Exhibits of the American Medical Association meetings in New York. The rat with ligated pylorus was found to secrete continuously and apparently spontaneously a large volume of acid gastric juice, the amount of extract which will inhibit this secretion by 50 per cent was tentatively defined as a unit of enterogastrone or urogastrone Later Shay et al noted that the rumen of the ligated stomach of the rat ultimately develops ulcerations and the prevention of these ulcerations was suggested as the basis of a test for anti ulcer activity

Evidence has been presented from several sources that the prevention of the

by chloroform has been found (Friedman unpublished) but these results are also difficult to interpret

Several methods for the preparation of a gastric secretory depressant from urine have been described It has been assumed, but as yet not proved, that all these various procedures yield the identical substance However, it is possible that more than one substance with inhibitory effects on the gastric glands and musculature may be excreted

The experimental ulcer which has been used widely and given much information is that produced in the dog by the so called Mann Williamson operation The duodenal contents, including the pancreatic juice, bile and succus entericus, are drained into the terminal ileum and the gastric contents are drained into the jejunum Animals subjected to this type of operation very

Table 8

SOURCE OF URINE	PER CENT INHIBITION
Human urine from	
Normal subjects	67 5
Duodenal ulcer	65 0
Gastric ulcer	49 6
Gastric cancer (achlorhydric)	52 3
Pernicious anemia	61 1
Canine urine from	
Normal animal	63 0
Gastrectomized animal	45 9
Enterectomized animal	56 0

The inhibition of gastric secretion during three hours following the intravenous administration of the urine extract is expressed as per cent of the secretion in control experiments during the same period Assay procedure acute experiment using the total gastric pouch of the dog receiving histamine (Friedman and Sandweiss 1941)

rarely live longer than one hundred days and nearly always die with a perforation or other evidence of ulcer formation at the gastrojejunal anastomoses

Sandweiss, Saltzstein and Farbman reported in 1936 that extracts of urine would protect against development of ulcers in dogs subjected to the Mann Williamson operation Since they used urine from pregnant women, and peptic ulcer is a very rare occurrence during pregnancy (Bernstein and Friedman, 1948), these investigators believed at first that they were dealing with a sex hormone However, subsequently we reported that extracts of urine from normal men and normal nonpregnant women also protected against experimental ulcers It is of extreme interest and importance to note that this ulcer-protective factor was found to be absent from the urine of patients with duodenal ulcer (Table 9) These experiments have been confirmed in other laboratories

Equally good results have since been obtained by Ivy and coworkers in the

Factors Inhibiting Gastric Motility

G M D E —gastric motor depressant of enteric origin
G M D U —gastric motor depressant of urinary origin
etc

Factors with Anti ulcer Activity

Anthelone e —anti ulcer factor of enteric origin
Anthelone u —anti ulcer factor of urinary origin
etc

A particular intestinal or urinary extract may contain, and at present nearly always does contain more than one of the above factors Furthermore, nearly all extracts designed for treatment of peptic ulcer, particularly those available commercially, contain substances in addition to the above such as gastrin, secretin, histamine like bodies, etc Consequently, in view of the impurity of such preparations it is strongly urged that these preparations be designated as concentrates, such as enterogastrone concentrate urogastrone concentrate, etc or better still, G S D E concentrate, anthelone u concentrate etc

The terms enterogastrone and urogastrone signify substances of enteric and urinary origin respectively which act to depress gastric function Since in patients receiving intestinal and urinary extracts the ulcer is located in the duodenum and improvement if any, would probably occur through a process of healing involving local stimulation of tissue proliferation, or perhaps as a process of immunization against ulcerogenic agents, it would be preferable in ulcer therapy not to employ the terms at all

CLINICAL STUDIES

In man enterogastrone preparations either orally or parenterally, have been found to be either ineffective or less potent than in animals in depressing gastric secretion Ivy and coworkers reported that enterogastrone in the doses used in treatment of peptic ulcer had no effect on gastric secretion Pollard Block and Bachrach also found gastric secretion in ulcer patients to be unaffected by repeated daily oral or parenteral administration of enterogastrone According to Kirsner et al, the effect of large (1 to 3 gm) intramuscular-administered doses of enterogastrone was reduction in the acid concentration of the nocturnal gastric secretion but the inhibition was variable and unpredictable Sandweiss Sugarman and Lockwood used the alcohol test meal in 9 ulcer patients receiving enterogastrone therapy acid concentration was reduced in 4 unchanged in 3 and elevated in 2 The results obtained by Ferayorni Code and Murlock are essentially in agreement with the above as much as 400 mg of enterogastrone intramuscularly and 18 gm orally had no significant effect on the gastric secretory response to a modified Ewald meal

Extracts of human pregnancy urine were found to have little effect on human gastric secretion when administered subcutaneously or intramuscularly

rumenal ulcer in the pylorus-ligated rat is associated with a decrease in the volume, acidity and peptic activity of the gastric content There is strong evidence to believe that while some substances and some diets, such as a high protein diet, may have a direct anti-ulcerogenic effect, most intestinal and urinary extracts which protect against the development of the rumenal ulcer do so chiefly, and perhaps solely, because they depress the gastric secretion In pylorus-ligated rats receiving urine extracts, ulceration of the rumen was induced by introducing into the stomach a quantity of gastric juice equal to that secreted by the stomach of control rats not receiving urine extract (unpublished data) The *point of these remarks is this assays of anti-ulcer activity* on the bases of ulcer prevention in the rat rumen are misleading since they evaluate indirectly only the secretory depressant activity of the extracts

We believe that there is a great need for a method which will test the ulcer preventing and or the ulcer-healing potency of the extracts independently of their influence on gastric secretion Recently it was proposed by Frederick and Greengard that the healing of gastric ulcers produced by subserosal injection of phenol be used, however, in our hands this procedure has not been found satisfactory (Waldron and Friedman, unpublished) Grossman has advocated as an index of anti ulcer potency the degree of healing of gastric mucosal defects produced by excision, this procedure or one similar to it may hold some promise of usefulness At present we are engaged in evaluating the use of the mouse for such purposes (Friedman and Larson, unpublished)

NOMENCLATURE

Some degree of confusion has arisen in the matter of designation of intestinal and urinary extracts Recently Sandweiss made the suggestion that the anti-ulcer factor in urine be called *anthelone*, to distinguish it from the gastric secretory depressant factor This is a distinct step forward but further clarification is needed In addition to duodenal and urinary extracts, extracts of other tissues have also been reported to depress gastric secretion or to accelerate tissue repair A gastric secretory depressant has been reported in achylic gastric juice (Brunschwig et al, 1939) and milk (Friedman unpublished), while a muscle extract has been reported to offer some protection against the experimental Mann-Williamson ulcer (Saltzstein, 1949) The following simple scheme of nomenclature is suggested for tentative use until the chemistry of the active principles in the extracts and their interrelationships become known

Factors Inhibiting Gastric Secretion

G S D E—*gastric secretory depressant of enteric origin*
G S D U—gastric secretory depressant of urinary origin
G S D G—gastric secretory depressant of gastric origin
G S D M—gastric secretory depressant of milk origin
etc

regimen gave the most favorable response No particular benefits from ' enterogastrone were noted The results of this study are not in agreement with those of Greengard et al

A protein free preparation from both gastric and intestinal tissue, called robuden ' has been used in Switzerland for several years Treatment consists of a series of 20 to 30 daily intramuscular injections of a water-soluble fraction together with the oral administration of a water insoluble fraction For gastric ulcer 70 per cent of the material is said to be derived from the stomach while for duodenal ulcer 70 per cent is derived from the intestine No information is available (or obtainable) as to the nature of the extraction procedure, the portion of intestine or even the species of animal used (presumably several species are used) The reports of treatment have been enthu-

Table 10 Comparative Effects of Parenteral Treatment of Chronic Peptic Ulcer Patients with Various Substances (Sandweiss et al 1948)

TREATMENT	NO OF PATIENTS	IMMEDIATE RESULTS		FOLLOW UP		
		NO OF ULCER ATTACKS TREATED	NO IMPROVEMENT %	NO OF ULCER ATTACKS FOLLOWED UP	RELAPSES WITHIN 6 MONTHS %	RELAPSES WITHIN 12 MONTHS %
Diet alkali regimen ambulatory	55	55	12	26	35	54
Histidine	43	43	28	21	86	90
Distilled water	22	22	14	13	67	92
Urine extract	63	83	11	44	38	64
Enterogastrone	42	42	36	23	43	70

siastic (see summary in Table 11) However no control studies have ever been reported, the improvement appears to be mainly symptomatic and in most cases the follow-up period was too short for certain evaluation The studies have all been made in Switzerland, have nearly all been published in the same journal, and nearly all show absence of a critical objective attitude

Sometimes crude extracts of tissue are found to be more potent with respect to a given pharmacologic or physiologic action than are purified extracts This is particularly true where the extraction procedure is difficult or the assay method unreliable Examples of this sort are found in the use of the digitalis leaf and crude liver preparations The possibility that whole intestinal substance similarly might prove more effective than a purified extract led us to attempt therapy with dried defatted whole duodenum (Wirts and Friedman 1949) One series of patients took 10 to 12 gm of duodenum sub

in small doses (Felson and Schiff, 1939) In this respect the results were comparable to the animal studies of Friedman and Sandweiss Only comparatively large doses of normal human urine extract when administered intramuscularly were found by Sandweiss et al to effectively depress both the histamine induced and the nocturnal gastric secretion in normal subjects and ulcer patients Direct instillation into the duodenum of a large quantity of normal human urine extract did not affect in 3 ulcer patients the course of gastric secretion induced by a modified Ewald meal (Friedman, unpublished) Recently Kirsner et al reported that intragastric administration to ulcer patients of as much as 7 5 gm of an extract of pregnant mares' urine was without influence on the volume, concentration and output of acid in the twelve hour nocturnal or the continuous thirty-six-hour gastric secretion

These studies all lead to the conclusion that extracts of intestinal mucosa and of urine are both much less effective in man than in animals as depressants of gastric secretion However, rigid comparison between the human response and animal response cannot be made in most cases since the extracts were administered to humans by intramuscular and oral routes whereas in animal experiments the usual route of administration was by vein At present the extracts are still insufficiently purified to justify their intravenous administration in man Another reason for the differences between animal and human experiments, particularly in those conducted with intestinal extracts, lies in the use of different preparations Most of the animal experiments were performed with preparations made in small amounts in institutional research laboratories, while the human studies apparently were carried out with preparations made in less rigidly controlled commercial plant laboratories

In 1944 Ivy reported on the effects of intramuscular administration of *enterogastrone in a group of 32 patients under observation for a period* of six to fourteen months In 20 of the patients ulcer management was continued for some time after commencement of "enterogastrone therapy The over all response was favorable but Ivy did "not believe that enterogastrone therapy, as used in these patients, provides as rapid and complete relief from distress as strict ulcer management

Greengard, Atkinson, Grossman and Ivy later reported on the treatment of 58 ulcer patients with enterogastrone Of 26 patients receiving injections daily, none showed failure to obtain symptomatic relief and only 4 patients had recurrent ulcer attacks The remaining 32 patients received injections three times per week Failure to obtain symptomatic relief was incurred in 2 patients and recurrences of ulcer attacks were limited to only 6 patients

Pollard and coworkers studied the roentgenographic appearance of the ulcer site in 17 patients who were given "enterogastrone therapy for peptic ulcer The ulcer lesion was found reduced in 6 cases, unchanged in 8 cases and worse in 3 cases

The studies of Sandweiss, Sugarman and Lockwood are particularly interesting These workers compared their data on 42 patients receiving 'enterogastrone with those obtained in patients receiving other forms of therapy The results are summarized in Table 10 It is to be noted that a diet alkali

the results of different investigators There are different opinions and standards of what constitute a favorable therapeutic response The disappearance of ulcer pain the prevention of recurring attacks of ulcer distress, the reduction in the duration of the exacerbation the degree of ulcer healing as determined by x ray, and the time taken for such healing have all been used as criteria Some reports are based largely on the subjective impressions of the patient, apparently without due consideration being given to the factor of suggestion The patient who is aware that the physician is giving him something new for his ulcer is actually receiving some form of psychotherapy and this factor must be recognized by the investigator

Table 12 Treatment of 62 Patients with Duodenal Ulcer for One Year

TREATMENT	NO OF PATIENTS AND SEX	X RAY EVIDENCE OF ULCER			NO ULCER ATTACKS PER YEAR	
		PRESENT BEFORE TREATMENT	FOLLOWING TREATMENT			
			NO EXAMINED	PRESENT	BEFORE*	DURING*
Dried defatted whole duodenum substance daily plus diet	34 (28 M 6 F)	29	17	4	1 to 7 (3 0)	0 to 2 (0 4)
Placebo daily plus diet	12 (7 M 5 F)	11	8	0	1 to 6 (3 2)	0 to 1 (0 1)
Diet only	16 (13 M 3 F)	15	10	1	1 to 6 (3 3)	0 to 2 (0 5)

* Figures in parentheses are averages

In studies on the therapeutic specificity of a substance for peptic ulcer the question frequently arises whether the patient as well as his ulcer should be treated The demonstration of functional and psychosomatic factors in peptic ulcer leads to the conclusion that these superimposed on organic biologic and biochemical factors, make the ulcer patient a difficult subject for study The evaluation of the clinical results of ulcer therapy with extracts of intestinal mucosa (such as enterogastrone, robuden) and urine (urogastrone, anthelone kutrol) thus presents formidable difficulties

Peptic ulcer is a disease characterized by apparently spontaneous periods of remissions and exacerbations and the patient is extremely responsive to

stance daily, a second series took a similar amount of enteric-coated lactose tablets, and a third series was on a bland ulcer diet alone Our results to date have been summarized in Table 12 and show no evidence of anti-ulcer activity peculiar to the duodenum substance

Reports on the intramuscular use of urine extracts in human patients with peptic ulcer have not been numerous The first study was that of Sandweiss and Friedman in 1940 They reported encouraging immediate results in a series of 20 patients Subsequently they reported a recurrence rate of 64 per cent in 63 patients after one year s treatment This was not as good a response as to diet-alkali therapy but better than to nonspecific therapy (Table 10) The extracts were prepared from the urine of normal women Recently Bercovitz, Page and Heffner reported encouraging results with extracts pre pared from the urine of the pregnant mare Symptomatic improvement and

Table 11 The Effect of Robuden in 154 Patients with Duodenal Ulcer

AUTHOR	NO OF PATIENTS	RESPONSE	
		SYMPTOM FREE	IMPROVED
Schmassmann H	26	11	11
Neumann H	25	20	4
Keiser D	16	4	9
Kapp H	34	29	5
Surkes A W	41	17	13
Hubacher O	15	13	2

The duration of treatment varied greatly as did the follow up period Roentgenologic evidence of improvement when presented by the author usually was less striking than the symptomatic evidence

radiologic evidence of disappearance of the ulcer were shown by the ulcer patients who took the urine extract daily by mouth in divided doses

The improvement shown by the patients receiving either normal human urine or pregnant mares urine apparently cannot be correlated with any reduction in gastric secretion If these results in humans are confirmed, they would support the conclusion drawn in 1942 by Sandweiss and Friedman and more recently by Ivy, Grossman and their coworkers The healing of the ulcer lesion by extracts of tissue and urine is not dependent on the anti gastric secretory properties of these extracts, some factor other than the secretory depressant, having a more direct action on the lesion, appears to be respon sible The mechanism involved is not known but since in animal experiments pretreatment with effective preparations may afford adequate protection, it is possible that establishment of an ' immunity to ulcerogenic agencies is involved

No adequate explanation has been advanced for the discrepancies between

use test either directly (pouch dog method, pylorus ligated rat method) or indirectly (modified pylorus ligated rat method) the anti gastric secretory properties The method of choice is one which measures the degree of tissue proliferation induced in unit time by unit concentrations of extracts

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changes in environment and to emotional conflicts A great number of patients have been known to respond to injections of nonspecific substances, such as milk proteins, typhoid vaccine and even distilled water This makes it necessary that clinical testing of each extract be carried out under rigid con ditions and with an adequate series of control studies This point has not always been appreciated As Hollander and Mage have pointed out, an unsuc cessful case always remains unsuccessful but a 'successful case may become a failure at any time Consequently, it is advocated that the efficacy of a therapeutic agent should be based on an index of failure, and that large series of both treated patients and control patients be followed over a long period of time

CONCLUSIONS

We must conclude that the results of treatment of human peptic ulcer with intestinal and urinary extracts have not been very encouraging No prepara tion has yet been found which gives as prompt and as sustained a response as does a diet-alkali regimen The markedly beneficial effects noted in the therapy of experimental animal ulcers stand out in sharp contrast The fol lowing suggest themselves as a few of a number of possible explanations for this discrepancy between clinical and experimental results

1 The extracts are administered to the patient in inadequate dosage Prob ably this is not the explanation and it is doubtful whether the patient can tolerate larger doses The side reactions with the present dosage level in many instances are severe and increasing the dose seems unwarranted

2 Commercial preparations of extracts, especially intestinal extracts are insufficiently purified and concentrated with respect to the anti ulcer factor and are contaminated by substances giving undesirable perhaps ulcerogenic, reactions For example, an enterogastrone concentrate available commercially has been found to contain gastrin and to cause strong motor activities of the gastrointestinal tract

3 The phenomena of tachyphylaxis and refractoriness develop making the patient no longer responsive These are subject to proof only if evidence is obtained that the patient responded to initial treatments and not to subsequent treatments with a particular extract Although in studies on gastric secretion and motility a refractory phase has been encountered in dogs receiving enterogastrone (Gray, Ivy, et al) and ' urogastrone (Bourque, Friedman, et al), no refractoriness to ulcer healing appears to have been reported in dogs with experimental ulcers

4 The duodenal ulcer occurring in man may be unlike most types of animal ulcer hitherto produced by experimental means Human peptic ulcer may be an inborn error of metabolism This makes questionable the value of con tinuing to treat human ulcer patients with extracts which have been found effective in experimental ulcers

5 The assay of the therapeutic index of an extract should be based on the ability to heal the ulcer rather than depress gastric secretion or motility This may be the crux of the problem Most routine assay procedures at present in

gastric pepsin While acid pepsin gastric juice has always been correlated with the active ulcerative process, it must not be implied that acid and pepsin singly or in combination even in high concentrations, are of themselves primary etiologic factors, although they may be The fact that gastric contents of high acidity and peptic power exist in many persons without peptic ulcer strongly suggests that an associated etiologic agent may be the deciding factor in the initiation of the lesion In such instances it seems probable that acidic gastric juice, when present, is forever ready to start its process of devitalization and ulceration, but its traumatic activity is being suppressed by other more powerful agents or mechanisms which create a condition adverse to ulceration

The concept that acidic gastric juice is the one indispensable factor in the production and maintenance of a chronic ulcer has led to the doctrine that, among other things, prophylaxis and therapy of the ulcer should be directed toward reducing the acidity or peptic power of the gastric juice before it comes into contact with the site of the lesion Such a doctrine obviously does not give attention to whatever underlying disease process may be responsible for establishing conditions which permit initiation of the ulceration It does not consider tissue resistance, circulation lack of intestinal or gastric mucus hormones or chalones infection, enterogastric mechanisms psychogenic influences acting centrally or locally, or any other condition or combination of conditions which has been incriminated as being a part of the disease of peptic ulcer The doctrine deals only with that one common link in the chain of events which leads to the formation and maintenance of all chronic peptic ulcers namely, proteolytic gastric juice

The principle of treatment which supports such a doctrine may be approached in several different ways, e g , by (1) inhibiting the digestive power of the gastric juice as secreted, (2) reducing the volume of gastric juice secreted, (3) neutralizing the gastric contents or (4) preventing contact of gastric juice with the ulcer Some of the means which are designed to accomplish this type of treatment consist of (1) specific gastric secretory depressants, (2) neutralizers of acid or pepsin, (3) removal of a large portion of the acid-secreting area of the stomach and antrum, plus gastroenterostomy, i e , a conventional type of subtotal resection (4) gastroenterostomy alone, (5) bilateral vagotomy, and (6) bilateral vagotomy combined with gastroenterostomy * In addition to the influence which these measures have on gastric secretion all but the neutralizers and gastroenterostomy also depress gastric motility, which

* The term bilateral vagotomy is defined as the transection or partial resection of both right and left vagus nerve trunks and their branches on the lower esophagus Complete vagotomy' is defined as sufficient disruption of vagal secretory fibers to the stomach so that subsequent insulin hypoglycemia is not accompanied by an increased rate or acidity of gastric secretion. A vagotomy which does not abolish this secretory response to insulin hypoglycemia is considered as incomplete Presumably a relatively few intact vagal secretory fibers which retain continuity with the stomach are capable of producing a secretory response to hypoglycemia. When performing a bilateral vagotomy it is always the intent of the surgeon to achieve a complete vagotomy

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THE EFFECT OF VAGOTOMY ON HUMAN GASTRIC *SECRETION*

ARTHUR M SCHOEN, M D *

THE ROLE OF GASTRIC SECRETION IN PEPTIC ULCER

Numerous agents, processes and conditions have been proposed as etiologic factors in chronic peptic ulcer † However, only one single factor, which can be altered so as to prevent or heal a lesion in most instances, has been demonstrated to exist concurrently with the presence of every active ulceration That factor is the ability of the stomach to secrete hydrochloric acid The fact that acidic gastric juice has been demonstrated in response to histamine in every person with active peptic ulcer who has been so studied, and the absence of active ulcer in the presence of a demonstrated histamine achlorhydria, has led to the belief that acidic gastric juice is the traumatic agent which produces and maintains the lesion per se This belief is based on both clinical and laboratory evidence which shows that peptic ulcers not only can be averted but will also heal more rapidly if the acidity of the gastric contents is held at a sufficiently low concentration for an adequate period of time The assumption is also made, in the case of duodenal ulcer, that the duodenal contents, as they impinge on the ulcer bearing area, are rendered sufficiently acidic by the gastric chyme so that the corrosive power of the mixed secretions is retained *Although the hydrochloric acid of the gastric secretions is the constituent* which has received the most attention, it is now generally conceded that its role in peptic ulcer lies not so much in its inherent corrosive ability, but rather in its capacity to produce a satisfactory medium for the proteolytic action of

* The original data reported herein are part of an investigation carried out in the Department of Pharmacology of the University of Louisville School of Medicine Louisville Ky which was supported in part, by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health U S Public Health Service The vagotomies were performed by Dr R Arnold Griswold Department of Surgery, University of Louisville

† The term ' chronic peptic ulcer is here used to define any ulcer which occurs only in those parts of the intestinal tract which come into contact with acidic gastric juice It does not include gastric or esophageal ulcers

ously without the aid of extrinsic stimulation has not yet been investigated sufficiently to permit a satisfactory answer Data which have been collected suggest that, under fasting conditions, the stomach of man in most instances continuously secretes at least small amounts of gastric juice This is in contrast to the findings in nonoperated dogs and cats, because under fasting conditions their stomachs do not secrete spontaneously

INFLUENCE OF SUBTOTAL RESECTION ON GASTRIC FUNCTION

The surgical treatment of peptic ulcer, whether it be subtotal resection with gastroenterostomy, gastroenterostomy alone or vagotomy, is designed solely to heal and prevent the recurrence of the lesion None of these procedures is devised to cure some associated disease which may be considered as an etiologic counterpart The surgical approach to prophylaxis and therapy is intended to produce two permanent physical changes relative to gastric function These are (1) a reduction of the peptic power of the gastric contents and (2) either a reduction of the impact of gastric contents on the intercepting intestinal mucosa or a complete diversion of the stream away from the initial lesion Subtotal resection of the Polya, Hofmeister or similar type which removes the pyloric antrum and a variable amount of the body of the stomach, usually, but not always, accomplishes both these objectives Peptic power is reduced because a part of the secretory surface is removed This results in a reduction of the volume of gastric secretions which in turn permits more effective intragastric neutralization and dilution of the gastric juice by food, saliva and regurgitated intestinal contents Subtotal resection removes the gastric antrum which, as already mentioned, is the site of formation of gastrin Unfortunately the fundus which remains and which retains its vagal innervation is the greatest source of the corrosive acid and pepsin secretions, and the antrum which is removed by subtotal resection, is the greatest source of alkaline mucus which is a protective secretion

The effect which the conventional present day subtotal resection has on the intestinal phase of gastric secretion is uncertain The gastrojejunostomy which accompanies subtotal resection completely diverts all the gastric contents away from the duodenum, thereby abolishing forever the protective gastric secretory depressant mechanism which is initiated by acidic gastric juice in the duodenum It has been shown by Pincus Thomas and Rehfuss (1942) in dogs with a Pavlov pouch and gastric and duodenal fistulas that the introduction into the duodenum of N 10 or N/15 hydrochloric acid was followed by a depression of pouch secretion providing the pH of the duodenal contents fell to 2 5 or below Other investigators have demonstrated that this inhibitory effect is less marked if the acid is introduced into the jejunum instead of the duodenum It has also been demonstrated by Thomas and Crider that the presence in the dog s duodenum of certain food substances, or their products of digestion is followed by inhibition of gastric motility These authors referred to this phenomenon as the enterogastric reflex and suggested that it depended on the integrity of the inhibitory apparatus of the vagus Other investigations carried out on human beings by Shay et al (1942) have demon

is a factor not to be overlooked when evaluating the mechanism of their beneficial effect on the healing of an ulcer

MECHANISMS WHICH REGULATE GASTRIC SECRETION

Before discussing some of the more obvious effects on gastric function which occur following a conventional type of surgical procedure for peptic ulcer, it is best to consider first the mechanisms concerned with the regulation of gastric secretion Although the questions "Why does the stomach secrete? and ' What determines the composition of the gastric juice? have not as yet been answered completely, sufficient evidence has been obtained from human beings and lower animals which shows that there are three mechanisms by which the gastric glands are stimulated These are known as (1) the cephalic phase, also called the nervous or psychic phase, (2) the gastric or hormonal phase and (3) the intestinal phase, sometimes called the secretagogue phase The gastric and intestinal phases are also known as the humoral phases because they act through the blood stream

The *cephalic phase* of gastric secretion stimulates the gastric glands reflexly through the vagus nerves The thought, smell or taste of food initiates impulses which are transmitted via the vagus nerves to the stomach These impulses are responsible for stimulating the gastric glands to secrete a juice which is high in peptic power, hydrochloric acid and total chloride, and fairly rich in mucus According to animal experimentation, the volume and quality of gastric juice produced by the cephalic phase is dependent on the intensity of the vagal stimulation (Vineberg, 1931)

The *gastric phase* of gastric secretion is initiated by the presence of food as well as other substances in the pyloric region of the stomach When such substances come in contact with the mucous membrane of the antrum, a hormone called gastrin is released by the antrum into the blood stream which is carried back to the stomach, stimulating the gastric glands to secrete a juice high in acid but low in peptic power

The *intestinal phase* of gastric secretion probably results from the absorption of digested foodstuffs from the intestine The quantity and quality of gastric juice produced by the intestinal phase depend on the amount and kind of products of digestion which are absorbed by the intestine

While these three mechanisms may act independently of one another, there is evidence to show that they also act synergistically, i e , the gastric response following the simultaneous action of either two or three of the phases is greater than would be the sum of the responses produced by each phase acting independently Thus, the rate of secretion and the composition of gastric juice are influenced by a combination of three independently or synergistically acting processes, each of which is initiated by specific stimuli and each of which is mediated by means of specific agents Gastric secretion is also affected by a depressant mechanism originating in the duodenum This will be discussed when considering the effect of surgical procedures on gastric function

The question of whether or not the human stomach can secrete spontane

omy plus gastroenterostomy, just as subtotal resection of the conventional type, also takes advantage of the reflux of alkaline duodenal contents into the stomach which produces further neutralization of gastric acidity This latter factor is sometimes overlooked when comparing vagotomy plus gastroenterostomy with subtotal resection

The statement has frequently been made that the response of a peptic ulcer to vagotomy plus gastroenterostomy should not be compared with the response to subtotal resection, but that vagotomy alone should be evaluated However, it must be borne in mind that a conventional subtotal resection is *always* accompanied by gastroenterostomy, and consequently a proper comparison between subtotal resection and vagotomy can be made only if similar adjunct procedures accompany each type of operation i e, only if both are accompanied by gastroenterostomy

CONVENTIONAL METHODS FOR MEASURING GASTRIC SECRETION

To evaluate properly the effect of vagotomy on human gastric secretion and emptying it is necessary not only to test these two functions under so-called basal conditions before and after vagotomy, but also to test the gastric response following the administration of proper stimulants which (1) show that the stomach is capable of secreting hydrochloric acid, and (2) show that it does or does not respond to an agent which is accepted as a central stimulant to the vagus nerves

The two most common methods for testing for adequate or ' complete vagotomy are (1) intermittent aspirations of a sample of gastric contents every fifteen minutes following the intravenous injection of regular insulin, and (2) measurements on nocturnal secretions collected during a twelve hour period Samples obtained by the intermittent method are analyzed for acidity The night secretions are measured for volume and acidity The data obtained from intermittent aspirations, utilizing insulin hypoglycemia as a nervous stimulant for gastric function, are interpreted by Hollander as signifying a complete neurectomy particularly if, in repetitions of a technically satisfactory test at follow up examinations, the patient is capable of secreting hydrochloric acid, as shown by histamine, but fails to show an increase in acidity after the intra venous injection of 20 units of regular insulin, providing the blood sugar con centration falls to at least 50 mg per 100 cc The nocturnal suction method, according to Dragstedt indicates a complete vagotomy if there is a reduction in the volume of aspirated contents and a decrease of over 60 per cent in the total hydrochloric acid recovered

The underlying principle which governs the interpretations of these tests is that gastric function is stimulated by impulses originating in the brain, or reflexly, which are conducted to the stomach via parasympathetic nerves principally the vagus, and possibly by other cholinergic fibers which traverse the thoracic segments of the spinal cord

The nocturnal aspiration test is based on the assumption that during the night while there is no intentional external stimulus applied a variable amount of the gastric juice secreted is produced because of continuous stim-

strated that the presence of hydrochloric acid in the duodenum of a person without peptic ulcer was accompanied by a marked diminution in the acidity of the gastric contents These same investigators also demonstrated that the gastric acidity of a person with uncomplicated duodenal ulcer was not inhibited by the presence of low or high concentrations of hydrochloric acid solution in the duodenum In view of the favorable influence which the duodenal acid mechanism and the enterogastric reflex may have by depressing gastric acidity and motility, it seems possible that the failure, in some instances, of subtotal resection to reduce effectively the acidity of the gastric contents may be a result of having abolished these protective autoregulators of gastric function

High subtotal resection of the conventional type takes advantage of its accompanying gastrojejunostomy by permitting the alkaline duodenal contents to flow into the stomach, thereby reducing the acidity of the gastric contents before they are discharged against the jejunal mucosa Finally, subtotal resection, by diverting the gastric chyme away from the duodenal lesion, not only permits the duodenal ulcer to heal, but also probably reduces the momentum of the gastric contents as they are discharged from the stomach, since the peristaltic waves of the fundus are not as vigorous and powerful as the prepyloric waves

INFLUENCE OF VAGOTOMY ON GASTRIC FUNCTION

Turning now to the influence of vagotomy on the course of peptic ulcer, several factors of importance need to be considered It has been demonstrated by a large accumulation of clinical material that following adequate bilateral vagotomy, the majority of patients experience an immediate and dramatic relief of their pain and a rapid healing of the ulcer This favorable response is attributed primarily to the marked reduction in the peptic power of the gastric contents Motility is also less active after bilateral vagotomy, and this effect undoubtedly plays an important role in the healing process Whatever else vagotomy may do to heal or help prevent a peptic ulcer is not known

Bilateral vagotomy, without gastroenterostomy, produces a decrease in the rate of gastric secretion by reducing or abolishing the cephalic phase The smaller volume of gastric juice produced is more readily neutralized and diluted by food and alkaline secretions from the upper alimentary tract, thereby causing the peptic power of the gastric contents to be diminished The humoral phases are also reduced as shown by the response to an Ewald meal, intramuscular histamine, or the presence of meat extract in the intestine Vagotomy, by decreasing the peristaltic activity of the stomach, reduces the momentum of the gastric chyme as it passes through the pylorus This diminishes the force of impact of the gastric contents on the duodenal mucosa, and gastroenterostomy, when combined with vagotomy, produces a further reduction Vagotomy, unlike subtotal resection permits gastric juice to empty directly into the duodenum, and consequently, those duodeno gastric mechanisms which may operate to suppress gastric secretion and motility are not necessarily abolished as they are following subtotal resection Finally, vagot-

lowed saliva, regurgitation from the duodenum and gastric mucus itself, are better able to reduce the acidity of a small volume of acidic gastric juice than a larger volume, and consequently the acidity of the mixed secretions, i e, the gastric contents, is reduced The maximum volume recovered preoperatively was 2580 cc (Pt R. L) In the same individual postoperatively it was 110 cc, which is but 4 per cent of the preoperative value In another person, A F a colored female, the mean volume recovered during two preoperative tests was 384 cc (504 and 264 cc) and the postoperative value was 342 cc,

Table 13 Summary of Data Obtained by the Method of Twelve hour Continuous Nocturnal Suction

Number of persons studied—40 Number of tests performed—142

	PRE VAGOTOMY VALUES	POST VAGOTOMY VALUES
Mean twelve hour volume aspirated cc	1126	556
Mean pH of aspirated contents	1 40	2.34
Mean free acidity of aspirated contents clinical units*	39 5	4 6
Maximum volume aspirated in twelve hours preoperatively (Pt R L) cc	2580	
Volume aspirated in twelve hours postoperatively from Pt R L cc		110
Minimum mean volume aspirated in twelve hours preoperatively (Pt A F) cc	384	
Volume aspirated in twelve hours postoperatively from Pt A F cc		342
Maximum acidity preoperatively (Pt R. L) clinical units	105	
Acidity postoperatively from Pt R L clinical units		0
Minimum acidity preoperatively (Pt W S) clinical units	2 4	
Acidity postoperatively from Pt W S clinical units		1 4
Maximum mean acidity postoperatively (Pt J B) clinical units	65	
Acidity preoperatively from Pt J B clinical units		33 0

* Clinical units equal the number of cc of 0 1 N NaOH required to neutralize 100 cc of gastric juice Free acidity was determined with a glass electrode pH meter The pH readings were converted to clinical units by formula

a reduction of only 11 per cent One possible explanation for the very low preoperative volume aspirated from A F is that continuous suction failed to recover all the gastric secretion and permitted the remainder to empty through the pylorus Because of this possibility it would be desirable to avoid the use of continuous suction when attempting to determine the rate of gastric secretion

The maximum free acidity of contents recovered from any person preoperatively was 105 clinical units from Pt R L There was no free acid in the contents recovered from this patient in the only postoperative nocturnal aspiration

ulation of the acid-secreting cells by vagal impulses of psychogenic or neurogenic origin Consequently, the recovery of a large volume of gastric contents of high acidity would be indicative of intense vagal activity Furthermore if, after section of the vagus nerves, the nocturnal aspirations recovered were of low volume and acidity, it would be assumed that the vagotomy was complete Thus, the nocturnal test is conducted at a time when there is no intentional nervous stimulation of gastric function Contrary to this, the insulin test referred to previously is carried out during a period when the vagus nerves are being intentionally stimulated by insulin hypoglycemia In a person with intact vagi, gastric function is usually, but not always, increased by the hypoglycemia which is induced by the intravenous injection of 15 or 20 units of regular insulin After bilateral section of the vagus nerves, the failure of insulin hypoglycemia to cause an increase in gastric secretion is indicative of complete vagotomy

EFFECT OF VAGOTOMY ON NOCTURNAL SECRETION

To illustrate the early effect of bilateral vagotomy on the gastric secretion of persons with histories of peptic ulcer, the data obtained from 142 pre- and postoperative continuous nocturnal suction tests carried out on 40 persons are summarized in Table 13 All vagotomies reported herein were considered to be adequate as judged by clinical response and by comparisons of all pre- and postoperative tests With few exceptions, all tests were conducted within one week of the time of operation Each subject was permitted to have his usual noonday feeding At about 5 00 P M he was given a liquid diet After that time, and for the duration of the test, no other feedings were permitted, and smoking was prohibited At about 9 00 P M the patient was intubated, through the nose, with a No 16 gauge French gastric tube with apertures at 1-inch intervals in its distal 10 inches By fluoroscopy, the tip of the tube was adjusted to the most dependent part of the stomach The gastric contents were then aspirated and the stomach was lavaged several times with physiologic saline The patient was put to bed, and continuous suction equal to 2 inches of mercury (27 inches of water) was started Three grains of intramuscular sodium phenobarbital were given routinely at the start of all tests In some instances, a measured quantity of water was drunk during the test period (from 30 to 60 cc) Continuous suction was maintained for approximately twelve hours, at the end of which period the total volume of aspirated contents was measured for volume and acidity The exact duration of the period was measured, and the volume recovered per hour, corrected for any water which may have been taken, was multiplied by 12 and recorded as volume recovered per twelve hours

A summary of results is given in Table 13 which shows that the mean postoperative volume is about 49 per cent of the mean preoperative volume The free acidity was decreased to 12 per cent of its preoperative value The greater reduction in acidity as compared with the reduction in volume is generally considered to be a result of the smaller volume of gastric juice secreted The neutralizing and diluting substances which enter the stomach such as swal

lowed saliva, regurgitation from the duodenum and gastric mucus itself, are better able to reduce the acidity of a small volume of acidic gastric juice than a larger volume, and consequently the acidity of the mixed secretions i e , the gastric contents, is reduced The maximum volume recovered preoperatively was 2580 cc (Pt R L) In the same individual postoperatively it was 110 cc , which is but 4 per cent of the preoperative value In another person, A F , a colored female, the mean volume recovered during two preoperative tests was 384 cc (504 and 264 cc) and the postoperative value was 342 cc ,

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which was obtained twelve days after vagotomy Patient J B had 33 units of free acid three days before vagotomy, and 65 units two days after vagotomy However, three days after operation his free acidity was zero

USE OF A DILUTION INDICATOR FOR MEASURING GASTRIC FUNCTION

Any method which attempts to measure the rate of gastric secretion without accounting for the volume of gastric contents which inevitably escapes through the pylorus, cannot be relied upon as a means for obtaining quantitative data concerning the volume of gastric juice secreted It has been shown by experiment on dogs under anesthesia that a mean of 31 per cent or as much as 98 per cent of the gastric juice secreted in response to histamine and acetylcholine may be emptied through the pylorus during a sixty minute period while continuous suction is being exerted on a multiple aperture gastric tube This is direct evidence that continuous suction fails to recover a relatively large proportion of the gastric juice secreted Since this inherent *characteristic permits a variable and immeasurable loss of contents through* the pylorus, it is impossible to predict or estimate with any known degree of accuracy the percentage error which these suction methods introduce in attempting to measure the rate of gastric secretion This does not infer that data obtained by continuous suction methods are of no value for estimating the effectiveness of complete vagotomy to reduce the volume of gastric juice secreted, because in the usual instance, the pre- and postoperative volumes secreted are so widely divergent that a large deficiency can be tolerated in the volume of gastric contents recovered without creating an overlapping of the ranges of the pre- and postoperative volumes

In order to measure more accurately the rate of gastric secretion, a method has been devised whereby the volume of gastric contents which empties through the pylorus during a given period of time can be determined with sufficient accuracy to permit the calculation of the rate of gastric secretion as well as emptying This method, therefore, does not impose the requirement that no gastric content pass through the pylorus, because the method is designed to determine how much did pass through during a measured interval of time The principle of the method is based on the fact that if a known volume of isotonic saline containing a known concentration of colored substance (indicator) is placed in an empty stomach into which flows an unknown volume of secretion, while during the same period an unknown volume of contents is emptied through the pylorus, then the quantity of secretion which entered and the quantity of contents which left the stomach can be determined from four related factors, namely, the volume within the stomach at the beginning and end of the period, and the corresponding concentrations of indicator As with any quantitative method, there are specific assumptions which are made and whose requirements must be adequately fulfilled if sufficiently accurate data are to be obtained The requirements imposed by this method have been carefully examined by experiments on dogs and by investigations on human subjects The results of these studies show that the requirements are fulfilled satisfactorily The formulas which are used for calculating the volume secreted and the volume emptied are

$$\text{volume secreted} = (V \;\; - V_t)\left[\frac{\log C \;\; /C}{\log V_t/V}\right] = S \text{ and}$$

$$\text{volume emptied} = V \;\; - V_t + S \text{ where}$$

V = volume of isotonic indicator solution injected into the empty stomach,
V_t = volume of contents present in the stomach at time, t,
C = concentration of indicator in V , and
C_t = concentration of indicator in V_t

EFFECT OF VAGOTOMY ON THE GASTRIC RESPONSE TO INSULIN HYPOGLYCEMIA

By use of this method gastric function has been studied in persons before and after vagotomy and in response to insulin hypoglycemia All tests were performed during the morning and following a twelve or fourteen hour fast The subjects were intubated with a fenestrated gastric tube and fluoroscoped The fasting residuum was aspirated, the stomach lavaged with saline, and again emptied as completely as possible Aspirations were carried out with the patient in the upright and also while in several horizontal positions A known volume of isotonic indicator (phenol red) solution was then injected into the empty stomach, and after a suitable period of time, usually fifteen minutes the stomach was again aspirated completely of its contents After three control periods, 15 or 20 units of regular insulin were injected intravenously and the test was carried out for two to four or more hours during which time the stomach was emptied completely every fifteen minutes and a fresh isotonic solution of selected volume was injected Blood specimens were taken at appropriate intervals for determinations of blood sugar concentration During the entire test period, the patient sat in a comfortable chair with head tilted forward to facilitate the expectoration of saliva In some instances, continuous suction was applied to a dental aspirator to aid in the removal of saliva In addition to the calculation of secretory and emptying rates pH readings and peptic powers were determined on all specimens pH readings were obtained with a glass electrode and were converted to free acidity by formula Peptic powers were determined at a pH of 1 70 by a modification of the method of Mett The quantity of free acid and peptic units, which were secreted per minute was calculated by multiplying the secretory rate by the values for free acidity and peptic power of aspirated contents after they were corrected for dilution by the presence of phenol red solution

The results summarized in Table 14 represent the average of values for persons studied before and after complete vagotomy All tests were performed during a period of one month to twenty five months after operation (average = 12 2) In no instance in this group of patients where the insulin test was repeated a second time postoperatively, was there a return to the preoperative response The control values represent the average of the means for each person The values recorded for all maximum responses to insulin hypoglycemia were calculated from data obtained during the period of the maximum response of secretory rate

Table 14 Gastric Function before and after Vagotomy and in Response to Insulin Hypoglycemia

Average Values for all Persons Studied with Complete Vagotomy

	NUMBER OF PERSONS STUDIED		NUMBER OF TESTS PERFORMED		SECRETORY RATE CC /MIN		EMPTYING RATE CC /MIN		FREE ACIDITY CLIN UNITS[1]		FREE ACID UNITS/MIN [2]		PEPTIC POWER[3]		PEPTIC UNITS/MIN [4]	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Controls[5]	36	10	67	42	2 68	1 28	4 56	2 21	41 6	6 9	129	12 1	980	418	2280	610
Maximum responses to insulin hypoglycemia[6]	18	10	18	17	6 08	0 41	8 60	0 58	75 3	1 2	511	0 9	1620	486	10800	239

[1] One clinical unit of free acidity is equal to one milliequivalent of hydrochloric acid per liter Clinical units are the same as the number of cc of 0 1 N NaOH required to neutralize 100 cc of gastric juice Free acidity was determined with a glass electrode pH meter The pH readings were converted to clinical units by formula

[2] Free acid was calculated by multiplying free acidity by secretory rate and expressing as units per minute which is the same as microequivalents of free hydrochloric acid per minute

[3] Peptic powers were determined at pH 1 70 by a modification of the method of Mett

Peptic units per minute were calculated by multiplying peptic power by secretory rate

[5] The control values represent the average of the mean control for each person

[6] The values recorded for acidity and peptic power in response to insulin hypoglycemia were calculated from data obtained during the period of the maximum response of secretory rate

Table 14 shows that for the average of the control values in this group of patients, vagotomy reduced the secretory rate from 2.68 to 1.28 cc. per minute, a reduction of 52 per cent. Acidity and peptic power were reduced by 83 per cent and 57 per cent respectively. The rate of secretion of free acid, as recovered in the gastric contents, was reduced by 91 per cent. The secretion of peptic units was diminished by 73 per cent of the preoperative rate per minute. It is of interest to note that both the concentration and rate of secretion of free acid and peptic units were reduced by a greater percentage than was the secretory rate. This suggests that the rate of secretion of neutral or alkaline nonproteolytic secretions is affected less by vagotomy than are the secretions of acid and pepsin. Therefore, not only does vagotomy reduce the peptic power of the gastric juice* secreted, but by reducing the volume output, its concentration is more readily decreased after secretion by such diluting substances as saliva, food and regurgitated intestinal contents.

Emptying rate was reduced by 51 per cent. This refers to the rate at which the gastric contents, consisting of gastric secretions and injected indicator solution, were emptied through the pylorus or stoma. The emptying rate is dependent, among other things, on the volume of gastric contents, it being greater with larger volumes. During these tests, the volume of indicator solution injected at the start of each period was made approximately equal to the volume of contents removed by the previous aspiration. Therefore, these values for emptying rate represent those which occurred while the stomach contained a normal volume of residuum for the conditions of the test.

Table 14 also shows the maximum response to insulin hypoglycemia before and after vagotomy. The maximum response may be manifested as an increase or a decrease in function. Before vagotomy, insulin hypoglycemia increased the secretory rate from 2.68 to 6.08 cc. per minute. After vagotomy, hypoglycemia not only failed to increase the rate of secretion, but in each instance was accompanied or followed by a decreased secretion. The average decrease was from a control value of 1.28 to 0.41 cc. per minute. Similar responses occurred in all other secretory activities except the postoperative response of peptic power to the hypoglycemia, which showed a slight increase even after vagotomy.

Of the preoperative responses to hypoglycemia, peptic power was increased by 65 per cent, and free acidity by 81 per cent, but peptic units per minute was *increased by 374 per cent as compared with only 296 per cent for free* acid per minute. This suggests that the output of pepsin was increased probably more than that of hydrochloric acid, because all peptic powers were determined at the same pH value. However, since a certain amount of the hydrochloric acid which was secreted was neutralized, as it always is, by the alkali of the gastric juice and therefore cannot be measured, it cannot be stated with certainty that the output of pepsin was increased more than was hydrochloric acid. After vagotomy peptic units per minute was decreased by 61 per cent in response to hypoglycemia, but peptic power was slightly

* Gastric juice consists of a mixture of the secretions produced by the different kinds of cells of the gastric mucosa, such as the acid, pepsin and mucus secreting cells.

increased following the injection of insulin This is in contrast to a reduction of 93 per cent in the free acid secreted per minute, and 83 per cent reduction of free acidity in response to hypoglycemia

It appears from these data that the output of pepsin responds most to hypoglycemia before vagotomy and that 'basal' peptic power and its response to hypoglycemia are affected least by vagotomy It must be stressed that all peptic powers were determined at the same pH, viz , 1 70, and that the peptic power of the gastric contents as it exists within the stomach is markedly influenced by the acidity of the contents, i e , with decreased acidity there occurs a decrease in the peptic power For this reason, the peptic power of the gastric contents, as they exist in the stomach after vagotomy, is usually very low because of the low acidity which is generally produced by vagotomy

SUMMARY AND CONCLUSIONS

1 Histamine achlorhydria has never been unequivocally demonstrated to exist concurrently with active peptic ulcer, nor has proven active ulcer ever been observed in persons with histamine achlorhydria Thus clinical experience, plus laboratory data obtained from experimental animals, suggests that acidic gastric juice is a sine qua non for the development and maintenance of a peptic ulcer

2 Stimulation of the secretion of acidic gastric juice is influenced by three separately and synergistically acting mechanisms which are initiated by specific stimuli, mediated by particular agents, and which act via humoral or nervous pathways The three mechanisms, and their associated secretory response, are known as the cephalic, the gastric and the intestinal phases of gastric secretion

3 Inhibition of gastric secretion and motility is known to occur by an autoregulatory mechanism which depends upon the ability of the intestinal mucosa (particularly of the duodenum) to respond to sufficiently high concentrations of locally acting hydrochloric acid or food substances

4 The surgical treatment of peptic ulcer is designed to treat the lesion per se, either directly, by its removal, or indirectly by diminishing the peptic power of the gastric contents The latter effect may be accomplished by abolishing or reducing one or several of the three phases of gastric secretion The surgical approach to prophylaxis or therapy does not pretend to cure some associated disease or condition which may be considered as an etiologic counterpart

5 Gastroenterostomy does not alter any of the three phases of gastric secretion It reduces the peptic power of the gastric contents by permitting a reflux of alkaline jejunal contents into the stomach

6 Subtotal resection of the conventional type abolishes the gastric phase of gastric secretion by removing the pyloric antrum It also removes a variable amount of the acid-secreting gastric mucosa Unfortunately, it removes the chief source of alkaline gastric mucus, which is the antrum, but leaves intact the most potent source of corrosive gastric acid, which is the vagally innervated fundus The gastroenterostomy, which is always associated with

subtotal resection, offers the advantage of the alkaline reflux from the duodenum, but by completely diverting the gastric chyme, including acid and partly digested food, away from the duodenum, it diminishes the gastric inhibitory mechanisms which are called into play when the duodenal contents contain acidic chyme

7 Complete vagotomy abolishes the nervous phase of gastric function It also reduces, but does not abolish the humoral phases as evidenced by a lesser response to histamine, an Ewald meal or the injection of meat extract into the intestine The average basal secretory and emptying rates are each reduced by about 50 per cent Acidity and peptic power of the basal secretion are reduced even more, suggesting that vagotomy produces a greater depression of the acid and pepsin secretions than of the neutral or alkaline secretion Complete vagotomy produces a depression of basal function in response to insulin hypoglycemia as shown by a decrease in the secretory and emptying rates and a decrease in the amount of acid and pepsin secreted The post-vagotomy response of peptic power to hypoglycemia is slightly increased over the basal value if peptic power is determined at a pH of 1 70 However, since the average basal gastric acidity after vagotomy is about pH 2 2, the peptic power of the gastric contents as it exists within the stomach, is actually of a lower value

THE EFFECT OF VAGOTOMY ON GASTRIC MOTOR FUNCTION

THOMAS E MACHELLA, M D

In order to better appreciate the changes in gastric motility which may occur following vagotomy, one should keep in mind that the stomach has both an extrinsic and an intrinsic innervation The extrinsic innervation consists of the sympathetic and the parasympathetic The intrinsic innervation consists of the intramuscular and submucous plexuses of ganglion cells and nerve fibers, an important part of which is composed of Auerbach s plexus Despite the fact that the results of stimulation of the extrinsic nerves in animals are not always predictable and reported data are conflicting, it is generally accepted that the two systems are mutually antagonistic and that the parasympathetic is excitatory to the smooth musculature except to the sphincters, while the sympathetic has the reverse influence

Experimentally, section of the vagi has been reported to give rise to gastric dilatation hypotonus and delayed emptying In the human similar motor disturbances may occur after vagotomy and have been so reported from various clinics It is planned to demonstrate the motor disturbances observed following complete vagotomy (negative insulin test) and to describe a method of correcting them when they give rise to troublesome symptoms

GASTRIC MOTOR DISTURBANCES FOLLOWING "COMPLETE" VAGOTOMY

A PERISTALSIS

The first slide illustrates the type of apparatus which was used for balloon kymographic recording (Fig 95) The balloon should be inserted into and

Fig 95 Method of recording gastric peristalsis used for obtaining tracings in sub sequent figures The balloon should be placed into the antrum of the stomach under fluoroscopic guidance and kept there (Machella T E Hodges, H H, and Lorber S H in Gastroenterology, Vol 8 published by Williams & Wilkins Co Baltimore Md)

maintained in the antrum which is the motor end of the stomach in contrast to the fundus which is the secretory end

The second slide (Fig 96) illustrates the type of motor activity recorded from the antrum of a duodenal ulcer patient The peristalsis is hyperactive and on several occasions forced the balloon into the duodenum

Figure 97 illustrates a tracing made on the same patient after a complete vagotomy There is now a complete absence of gastric peristaltic activity

The fourth slide (Fig 98) illustrates the roentgen appearance of a stomach seventy-five minutes after the ingestion of a barium meal During the period of observation no peristalsis was observed in the atonic stomach

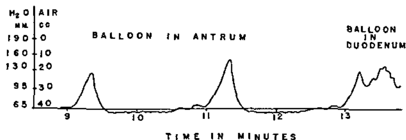


Fig 96 Balloon kymographic tracing of hyperactive antral peristalsis prior to vagotomy (Machella T E Hodges H H and Lorber S H in Gastroenterology Vol 8 published by Williams & Wilkins Co Baltimore Md)

M I N U T E S

Fig 97 Balloon kymographic tracing obtained with balloon in antrum eighteen days after transthoracic vagotomy There is a complete absence of peristaltic waves (Machella T E and Lorber S H in Gastroenterology Vol 11 published by Williams & Wilkins Co Baltimore Md)

It is evident, therefore, both from balloon kymographic recording and by roentgenoscopy, that a "complete" vagotomy can effectively abolish gastric peristalsis



Fig 98 Completely retentive stomach with absent peristalsis (Machella, T E, Hodges H H and Lorber S H in Gastroenterology Vol 8 published by Williams & Wilkins Co, Baltimore, Md)

B GASTRIC RETENTION

Gastric retention may follow a complete vagotomy Figure 99 illustrates the roentgen appearance of a postvagotomy stomach six hours after the ingestion of a barium meal Also evident is the atonicity and absence of peristalsis

The next slide (Fig 100) illustrates the appearance of the same stomach twenty four hours after ingestion of the barium meal About 50 per cent of the barium is still present in the stomach, the remainder is present in the colon

C. STATUS OF THE PYLORUS

The status of the pylorus following 'complete" vagotomy has not been settled Theoretically destruction of the parasympathetic innervation might be expected to cause the pylorus to go into spasm

Latarjet (1922) believed the pylorus to be patent However, his vagotomies, performed by the abdominal route, are regarded as having been incomplete

Paulson and Gladsen (1947), who studied their postvagotomy cases gastroscopically, found the pylorus to be patent but they saw it close when a peristaltic wave approached They did not report the results of the insulin tests on the patients so observed The occurrence of peristaltic waves suggests that the vagotomies were incomplete Furthermore, the influence of drugs, usually



Fig 99 Barium meal completely retained in stomach six hours after its administration (Machella T E Hodges H H and Lorber S H in Gastroenterology Vol 8 published by Williams & Wilkins Co Baltimore Md)



Fig 100 Retention of about 50 per cent of barium meal administered twenty four hours previously The remainder of the barium is in the colon (Machella T E Hodges H H and Lorber S H in Gastroenterology Vol 8 published by Williams & Wilkins Co Baltimore Md)

administered prior to gastroscopy played an undetermined role in what the observers saw

Churchill and Sweet (1942), who in their resections for carcinoma of the lower esophagus probably have performed rather complete vagotomies, believed the pylorus to be in spasm One of their patients, in whom the lower esophageal stump and fundus of the stomach were brought over the ribs through a subcutaneous route, was observed to have such a tightly closed pylorus that a pyloroplasty had to be performed

Our own feeling is that the pylorus is closed at least part of the time This is based on an inability to massage barium into the duodenum during fluoroscopy (Fig 99) and on the fact that during a twenty-four hour period, some barium does get out of the stomach (Fig 100) The problem requires further investigation

CORRECTION OF MOTILITY DISTURBANCES FOLLOWING VAGOTOMY

In postvagotomy patients, in whom the pylorus is the only outlet from the stomach, the problem of gastric retention may prove to be a serious one Nutrition is impaired, and a number of patients have had to have a second

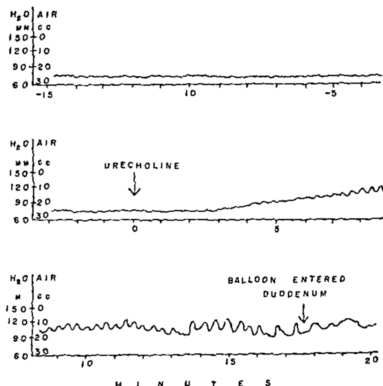


Fig 101 Balloon kymographic tracing on twenty first day after resection of fundus of stomach and lower esophagus for peptic ulcer situated high on the lesser curvature of the stomach Insulin test was negative Peristaltic activity was completely absent until it was induced by a subcutaneous injection of 5 mg of urecholine The induced motor activity was of sufficient intensity to force the balloon into the duodenum (Machella, T E and Lorber S H in Gastroenterology Vol 11 published by Williams & Wilkins Co , Baltimore Md)

operation performed for relief from retention The retention in our cases varied in duration from two to thirteen months, during which period gastric evacuation was promoted pharmacologically by means of the parasympathomimetic drug urecholine (Merck) The drug, when administered in adequate amount, will induce sufficient gastric peristalsis to evacuate the stomach (Fig 101) Equally effective is doryl (Fig 102)

When faced with the problem of gastric retention after vagotomy the following procedure is employed in our clinic The patient is given a barium meal and a careful study is made of the stomach, duodenum, jejunum and, if one is present, the stoma In the usual case, antral peristalsis is either absent

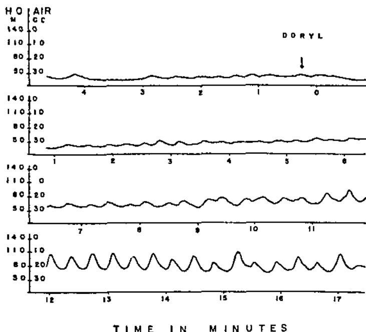


Fig 102 Increase in tonus and the appearance of contraction waves in the antrum after a subcutaneous injection of 0 3 mg carbaminoylcholine chloride (doryl Merck) The period of induced activity lasted approximately fifty minutes

or ineffective and barium fails to leave the stomach A subcutaneous injection of 5 to 10 mg of urecholine is then administered If this is followed by a gastric emptying and the passageway from the stomach through the duodenum and jejunum is not mechanically obstructed (Figs 103 104 105 and 106), the patient is placed on an oral test dose of 10 mg of urecholine before each meal He is then observed to determine whether the dose is too large or too small If the dose is too large diarrhea occurs if too small the retention persists The dose is then increased or decreased until an amount sufficient to promote satisfactory gastric emptying but not diarrhea is found Occasionally when gastric retention is complete, a subcutaneous injection of the drug must be given in the morning to promote the entrance of the drug from

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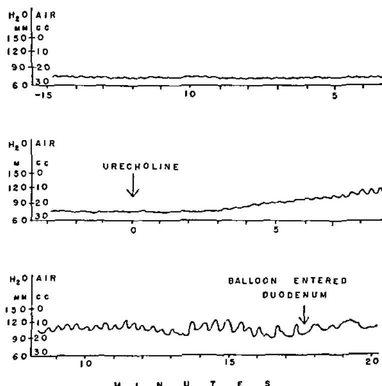


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the stomach into the intestine after which further subcutaneous injections may or may not be necessary Urecholine is administered regularly before each meal until such a time as spontaneous evacuation occurs, this is determined by repeated fluoroscopic observations of gastric emptying after omitting the drug for twenty-four hours, by the absence of symptoms of retention when a placebo is substituted, or by the patient himself learning that he no longer needs the drug In the absence of organic obstruction, the amount and frequency of urecholine administration can be gradually decreased as time goes on If obstruction of the duodenum occurs as a result of scar contraction at the site of the healing ulcer, the patient finds that increasing doses of urecholine are required to provide freedom from symptoms of retention

When evidence of organic obstruction is found initially or subsequently either at the site of the duodenal ulcer or at the site of gastroenterostomy stoma, the patient is referred for operative correction of the abnormality

Certain points concerning effective use of urecholine require emphasis, these are as follows

1 The tablets for oral use should be allowed to disintegrate in water before ingestion, otherwise they may remain in the stomach a long time before dissolving

2 The drug, when orally administered, must find its way into the small intestine to be effective We have not been able to demonstrate evidence of its sublingual or gastric absorption Any effect ascribed to sublingual administration probably is due to the fact that the drug is swallowed and finds its way into the small intestine where it is absorbed

3 Gastric evacuation is determined largely by the antral pump Urecholine will not evacuate a stomach unless the retention is capable of being corrected by making the antral pump work It will not evacuate retained material from the fundus of a stomach if its free passage into the antrum is interfered with as a result of a cascade or a marked hour glass deformity The drug exerts its gastric motor effect on the antral end of the stomach

4 The drug should not be administered to asthmatic patients as it is capable of constricting the bronchioles and precipitating attacks of asthma

5 The drug should be injected subcutaneously and not intramuscularly or intravenously as the side-effects following rapid maximum activity may be unpleasant These consist of flushing sweating, increased salivation, abdominal cramps and desire to defecate or urinate

6 The effects of the drug can be stopped by an injection of atropine, intravenously more rapidly than subcutaneously In this connection, it might be pointed out that urecholine won t work if the patient is receiving belladonna or other drugs with atropine like action

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Fig 103



Fig 104



Fig 105



Fig 106

Figs 103–106 103 *Roentgen appearance of stomach taken one hour after inges*tion of barium Insulin test was negative Ineffective minor peristaltic waves are present 104 Roentgen appearance of stomach five minutes after subcutaneous injection of 5 mg of urecholine A powerful wave can be seen traversing the antrum Barium is being forced into the duodenum 105 Roentgen appearance ten minutes after urecholine Most of the barium is in the jejunum 106 Roentgen appearance thirty minutes after urecholine Most of the barium is in the lower ileum and some *of it* has reached the cecum The stomach is practically empty Such rapidity of transport is undesirable and indicates that a smaller dose of urecholine orally administered will be sufficiently effective to evacuate the stomach (Machella T E and Lorber S H in Gastroenterology Vol 11 published by Williams & Wilkins Co, Baltimore, Md)

observed these complications in a very careful study of a relatively small group of patients

Bilateral vagotomy must at present be looked upon as an experimental operation For evaluation of its exact usefulness no more operations need be reported There have been enough done, but a longer period of follow up will be necessary, and a more careful study of those which have been per formed, before the role of this procedure can be properly determined

I might summarize our experience in this way A complete vagotomy is often difficult to attain There are many variations in the vagus distribution So-called complete vagotomy is now judged by the results of a carefully done insulin test This may or may not be the best means of judging the adequacy of the vagotomy Bilateral vagotomy is followed by gastric retention The retention may give rise to troublesome symptoms for as long as from two to twelve months It can be corrected or prevented by doing another operation—gastroenterostomy—or pharmacologically, by the use of such drugs as urecholine and doryl Gastric retention may prevent the prompt return of the patient to a useful way of life

Vagotomy has given satisfactory results in patients with marginal or jejunal ulcer and these we believe are its main indications at the present time Dr Dragstedt believes that if the operation is good for the worst of ulcers, why not use it for the best of ulcers?

An incomplete vagotomy, which may follow even the most careful dissection, plus a gastroenterostomy, may be followed by a marginal ulcer or by failure of the duodenal ulcer to heal Some surgeons are already using vagotomy as a means of reducing the extent of a gastric resection for duodenal ulcer It is my opinion that this is a totally unsafe procedure and I m sure Dr Ferguson will tell you that when you do a resection for ulcer you should really do a radical resection Vagotomy should not be used for gastric ulcer and it should not we believe, be used for bleeding duodenal ulcer It should not be used when pyloric stenosis is already present unless gastroenterostomy is done at the same time

The objective of any operation for ulcer should be to remove the ulcer, and to obtain a permanent reduction in free hydrochloric acid secretion In no other way can surgery offer at present a high percentage of cures

We have observed the following case A man was sent to us from Elmira New York with a longstanding history of duodenal ulcer and a persistent hypoproteinemia While in the hospital at Elmira three jejunal ulcers had been perforated It was impossible after the most careful type of therapy there to elevate this man s serum protein above 3 gm per 100 cc His gastric acid secretion was the highest and the largest amount we have ever seen Dr Machella after passing a tube down into his jejunum found that the concentration of acid in his jejunum was the highest that has ever been recorded in a patient This was an ideal case for a bilateral vagotomy The only reason the serum protein could not be elevated by any type of diet was because the acid concentration in his upper small gut was so high that the proteolytic

THE PRESENT STATUS OF VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER

(1) *The Surgeon's Viewpoint*

I S RAVDIN, M D

I should have liked to have heard what Dr Bockus is going to say about this operation which has been revived and elaborated so beautifully by Dr Dragstedt as a physiologic approach to certain factors which play a part in the initiation of peptic ulcer and certainly in its chronicity Previous speakers have told you that bilateral vagotomy whether done by the supradiaphragmatic or by the infradiaphragmatic route reduces gastric secretion and reduces the hydrochloric acid content of this secretion It relieves pain and it provides a biologic condition more conducive to healing of the ulcer It is, however, associated, as Dr Machella has told you, with a high incidence of postoperative gastric retention, which may be so severe as to become alarming, and in at least 75 per cent of our patients has proved to be, to say the least, most annoying

Let me start by saying that no gastroenterologist prior to operation, and no surgeon at the time of exploration, can tell with confidence whether a gastric ulcer is benign or malignant Vagotomy ought never be used as a method of therapy for a gastric ulcer I want to stress this because many vagotomies have been performed on patients with gastric ulcer, and there are already instances in which the operation was done on patients with gastric carcinoma To obtain a good result in 96 per cent of the patients with duodenal ulcer, the surgeon does not require vagotomy if he has done an adequate gastric resection It was proposed by one surgeon a few months ago that at the time the surgeon operates for a perforated duodenal ulcer he should at the same time do a vagotomy I mention that only to condemn it

Ruffin and his group have collected the data on many patients who have been partially or completely vagotomized at a level just above or just below the diaphragm They are collecting these data at a national level

We now know that division of the vagi above the stomach provides immediate relief from pain It does, however, in my opinion, superimpose a condition of delayed gastric emptying in most patients and in some instances a condition of massive gastric retention In others, there is produced an intractable diarrhea Gastric retention, the belching of foul-smelling gastric contents, and a persistent feeling of fullness which so many of our patients have had after operation are nonphysiologic conditions Reports are already available of perforation of the ulcer after vagotomy, of return of gastric acid secretion probably from incomplete section or from regeneration of the vagi, and of return of the ulcer, which had healed promptly after vagus resection We have

difficulty in maintaining normal nutrition Necheles sounded the following warning at a national meeting two years ago What do we know about the late effects of this denervation upon the function of important organs like the pancreas the liver and the small intestine?

It was unfortunate that the operation of vagotomy received so much premature publicity in the lay press This was responsible for many patients requesting, if not insisting upon a vagotomy who had never been adequately treated medically Furthermore the operation was at times unwisely performed for gastric ulcer and for duodenal ulcer complicated by plastering and by stenosis Obviously many of the latter group of patients required subsequent operative procedures These are some of the reasons conservative physicians and surgeons were loath to have many of their ulcer patients embark on the good ship vagotomy until the experiment had had a more thorough trial in a few clinics

ANTICIPATED BENEFICIAL EFFECTS OF VAGOTOMY

Let us briefly view the favorable effects which might be anticipated by the performance of vagotomy for ulcer cure This operation, if complete either abolishes or reduces the basal secretion of gastric acid and pepsin If the quieting of gastroduodenal motility and peristalsis is beneficial to ulcer disease then some beneficial effect should be derived from the operation providing this effect is permanent Some consideration may be given to less known effects which may prove advantageous to the ulcer patient One might cite the experiment mentioned by Stewart Wolf He observed vascular mucosal changes, hyperemia and congestion, in a subject as a result of psychic trauma (resentment, anger and anxiety), which could not be similarly reproduced after vagotomy It is conceivable that gastric vagal denervation may exert a beneficial effect in this way, if it is assumed that this mucosal effect may predispose toward the development of chronic peptic ulcer Further observations of this type are very desirable Obviously if it could be shown that psychic insult does bring about an effect on the mucosa which leads to peptic ulcer, psychotherapy would constitute a much more rational approach to therapy than severance of nervous connections between the brain and the stomach

Furthermore as we intimated yesterday, one wonders whether after vagotomy some anti ulcer substance in mucin or mucin itself might be secreted in larger mounts It seems strange that physiologists and surgeons who have had a large experience with vagotomy have not made a more careful study of the secretion of mucin following this operation A great increase in the secretion of mucin could be of some benefit to the ulcer bearing patient

PERMANENCE OF EFFECTS

These are some of the possible beneficial effects of vagotomy providing the effects were found to be lasting This brings us to a consideration of the question How permanent are the changes in the stomach brought about by vagotomy?

enzymes were incapable of acting physiologically He had a subdiaphragmatic vagotomy, and obtained the most temporary relief Another jejunal ulcer perforated Gastric acid secretion came back and a supradiaphragmatic vagotomy was done He still had a high concentration of free acid It was not until he had the most massive type of gastric resection that this man was restored to a useful life

The enthusiasm which greeted the advent of vagotomy should now be tempered by an attitude of cautious questioning It is useful in the treatment of marginal ulceration, a condition which is frequently associated with an operation of great magnitude and considerable mortality Whether even with a gastroenterostomy it will be proven to be better than gastrectomy for duodenal ulcer, or even as good, remains for the future to tell It is my opinion that as the months and the years roll by it will be used with less and less frequency and that in carefully studied comparable series of patients the results which will be obtained from an adequately done radical gastric resection will be found better than those obtained following vagotomy

THE PRESENT STATUS OF VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER

(2) *The Internist's Viewpoint*

HENRY L BOCKUS, M D

I should like Dr Ravdin to know that my opinion concerning the present status of vagotomy in the treatment of peptic ulcer coincides closely with the views which he has expressed In this country we have been witnessing an interesting experiment Twenty years from now I think it will be called the "vagotomy epidemic of 1943 to 1948" I say "to 1948" because it is becoming increasingly evident that vagotomy alone for the cure of peptic ulcer, except gastrojejunal ulcer, will not be employed in many clinics in the future

I may say that many, if not most conservative internists and surgeons looked with some trepidation upon this experiment from the beginning Conservative physicians having a broad view of the pathogenesis of peptic ulcer disease and those familiar with the physiologic principles involved in peptic ulcer surgery doubted if conditions essential to the surgical cure of ulcer could be brought about by vagal denervation of the stomach Achlorhydria was not anticipated Those familiar with previous animal and human experiments suspected that anything approximating complete vagectomy would bring about gastric stasis to a very marked degree It was feared that Pavlov's experiences with his early vagotomized animals might be reproduced in the human It will be recalled that it was with great difficulty that the animals so treated were kept alive for any period of time because of gastric retention and

surgery, providing the addition of vagotomy is easily accomplished without adding greatly to the technical difficulty of the operation The immediate results of this combined procedure at the Lahey Clinic as reported by Wilkinson have not been as satisfactory as partial gastrectomy alone A long comparative follow up is not yet available *

Now just one other thought I think we should keep an open mind about the value of vagotomy, perhaps combined with gastroenterostomy or pyloroplasty, in the treatment of the young patient who comes back every six months or a year with recurrent gastroduodenal hemorrhage and in whom one can never demonstrate a duodenal ulcer It has been assumed that the bleeding in many of these patients is the result of erosions or acute ulcers Partial gastrectomy has not proved satisfactory in the prevention of recurrences in many such patients Some observers believe that the results of vagotomy alone in the management of hemorrhage from duodenal ulcer are satisfactory Ruffin who is correlating statistics for the Committee on Peptic Ulcer of the American Gastro-enterological Association mentions an experience with 369 vagotomies on patients with a previous history of hemorrhage The recurrence rate of bleeding in this group to date is given as only 5 per cent Obviously the follow up period is too brief for an adequate appraisal of results to be anticipated with vagotomy in the treatment of gastroduodenal hemorrhage

If eventually vagotomy proves of some benefit in peptic ulcer management it is highly likely that invariably it will be combined with another surgical procedure to avert the troublesome gastric stasis which it so often provokes Personally I shall continue to employ an expertly performed partial gastrectomy rather than vagotomy in those patients with gastric or duodenal ulcer who require an operative procedure Vagotomy must remain an experimental procedure until the final results of a long follow up become available

POSSIBLE RELATIONSHIP BETWEEN HYPERTROPHY OF BRUNNER'S GLANDS AND HYPERACIDITY

WILLIAM H ERB, M D

Our interest in the relationship between hypertrophy of Brunner's glands and hyperacidity and peptic ulcer was aroused by the following case

R S L Hospital No 182529 A thirty six year old white male was hospitalized on November 3, 1947, because of roentgen evidence of multiple polyp-like projections in the proximal duodenum The polyps first were recognized seven months prior to hospital admission The only immediate subjective complaint was a tendency to loose stools which had been present

* In a recent communication Wilkinson reported a lesser incidence of recurrence of bleeding following gastrectomy combined with vagotomy than after gastrectomy alone

certainly unsatisfactory The gastric retention was complete without urecholine In less than two years following the vagotomy, a large gastric ulcer *developed*

Many surgeons who were originally enthusiastic about the employment of simple vagotomy no longer perform vagotomy alone except in the treatment of gastrojejunal ulcer following gastric resection I agree with Dr Ravdin that simple vagotomy is justified in the treatment of such patients, providing the original resection was an adequate one I am somewhat skeptical concerning the permanence of good results even in this group of patients However, the procedure is certainly justifiable since nothing else can be done in many of these patients except total gastrectomy

VAGOTOMY IN COMBINATION WITH OTHER OPERATIONS

Although vagotomy alone, because of the undesirable side effects, has been abandoned in most clinics, except for the treatment of gastrojejunal ulcer, the procedure is being recommended in combination with other operations In these clinics, infradiaphragmatic vagotomy in combination with gastroenterostomy or pyloroplasty is being employed for both complicated and uncomplicated duodenal ulcer Gastroenterostomy and pyloroplasty had been abandoned by many surgeons for the treatment of most duodenal ulcers because of superior results following adequately performed partial gastrectomy It will be interesting to see whether the addition of vagotomy to one or the other of these two operations will prove successful In preliminary reports the results are alleged to be satisfactory Available follow up studies are totally inadequate at present, since an insufficient time has elapsed following the operative procedures Personally I should prefer that these procedures be considered experimental and that they not be universally employed until a five year follow up from some of the larger clinics becomes available

This brings us to a consideration of the combined operation of partial gas*trectomy and subdiaphragmatic vagotomy for the patient requiring* ulcer surgery Perhaps I should begin my remarks in this way, that in my opinion partial gastrectomy properly performed as Dr Ferguson will emphasize a little later this morning, in our experience has proved to be an excellent operation Present statistics indicate that the recurrence rate of gastrojejunal ulcer following a properly performed partial gastrectomy probably does not exceed 5 per cent The poorest results from partial gastrectomy are in those patients *with gastric hypersecretion and Grade IV gastric hyperacidity* A postoperative achlorhydria is not to be anticipated in more than 60 per cent of those patients Obviously if the addition of vagotomy will increase the incidence of achlorhydria following gastrectomy, it should prove beneficial A long follow-up on partial gastrectomy combined with vagotomy will be required before we have the answer We must have further data bearing on the operative mortality of partial gastrectomy with vagotomy Does a satisfactorily *performed subdiaphragmatic vagotomy* add substantially to the risk of partial gastrectomy? At present we are trying the combined operation in alternate patients with gastric hypersecretion and hyperacidity requiring ulcer

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for about a year, numbering approximately four to six daily The stools varied from formed to watery consistency with an absence of recognizable mucus or blood Seven months prior to admission a severe secondary anemia was recognized elsewhere and apparently improved with the use of iron and liver preparations The past medical history otherwise was negative There was an 8-pound weight loss in the past year Physically the patient was asthenic, slight, somewhat pale and showed no obvious abnormality

Shortly before the present admission to the hospital roentgen examination of the duodenum by a barium meal revealed a number of small rounded opacities, which appeared more prominent than those reported seven months previously The polyp-like defects shown on roentgen study were confined to the duodenal cap and proximal portion of the descending loop of the duodenum No tenderness was elicited over the site of the defects Some of the prominence probably was more apparent than real due to the fact that duodenal compression technic was used in the later examination One of the polyp-like defects in the superior portion of the duodenal cap seemed much larger than the surrounding defects in comparing the two sets of films and suggested the possibility that it was, in fact, a growing tumor In retrospect, the altered appearance of the duodenal cap probably was related to uneven compression of that region during the examination, since the subsequent operative specimen revealed a surprising uniformity in the size and shape of the duodenal projections

Barium enema and a small bowel roentgen series were negative apart from moderate coarsening of the mucosal pattern of several of the proximal jejunal loops and slight dilatation of the small intestinal loops up to the region of the distal ileum There was an absence of roentgen defects elsewhere in the small and large bowel such as were seen in the upper duodenum

Fractional gastric analysis with an Ewald test meal showed a fasting acid of 127 units of free hydrochloric acid and 144 units of total acid The peak acid figures, occurring at one hundred and five minutes, were 150 units of free hydrochloric acid and 168 units of total acids

Because of the abnormally high acid titer of the stomach contents, a double-lumen tube was placed in the duodenum under repeated fluoroscopic guidance in order to simultaneously remove both the stomach and duodenal contents During a control thirty minute period 325 cc of gastric contents were removed and 167 cc of duodenal contents The titration values for the removed gastric and duodenal contents are recorded in Table 15 With the double-lumen tube in place 80 units of secretin were given intravenously with a response also recorded in Table 15

Attention is directed to the acid character of the fasting duodenal contents The response of the pancreatic enzymes and bicarbonate in the duodenal juice following the administration of secretin was regarded as normal

Gastroscopy on November 1, 1947, revealed a normally appearing gastric mucosa without evidence of polyposis The most distal portion of the antrum was not visualized

Routine blood count, sedimentation rate, prothrombin time, serum pro-

teins with A G ratio serum bilirubin, serum amylase, and lipase and serologic test for syphilis were all normal Five stools were examined for occult blood by Gregerson method, of which two were negative and three were +3

The patient was discharged on November 11 1947, and readmitted for operation December 8, 1947 One week prior to December 13 1947, he developed severe epigastric pain for the first time and vomited once The pain was sharp, griping doubled him up and was associated with loose stools

On December 13, 1947 laparotomy was performed by the author using a transverse incision The duodenum felt thick although single individual polyps could not be felt The pyloric sphincter was opened The mucosa of the duodenum was heaped up in folds A specimen of one of the folds was removed for frozen section which failed because of technical difficulties The mucosa

Table 15 Values for Gastric and Duodenal Contents Obtained by Use of Double Lumen Tube after the Administration of 80 Units of Secretin (Administered at 9 45 A M) (Study carried out by Dr Mack Lopusniak)

	FASTING		POST SECRETIN IN MINUTES			
	(A M) 9 15–9 25		0–10	10–20	20–40	40–60
Duodenal						
Volume	60	107	80	59	25	29
Icterus index	20	3	1	5	1	5
Total base in Eq /L	—	(acidity of 7 clinical units)	131 8	100 2	41	27 7
Gastric						
Volume	160	165	162		150	51
Free HCl	92	104	120		97	104
Total acid	112	125	132		115	128

seemed more normal near the ampulla of Vater Approximately 3 inches of the distal stomach and 3 inches of the proximal duodenum were removed in one piece In dissecting the duodenum free from the pancreas the outlet of the duct of Santorini was preserved The line of resection was 1 cm proximal to the ampulla of Vater The common duct was not injured A V shaped excision of the anterior wall of the stomach made the circumference of the stomach equal to that of the duodenum A routine two layer anastomosis was done using cotton for the outer layer and catgut for the inner layer The abdomen was closed in layers

The following pathologic report of the excised specimen was recorded The total length of the specimen is 15 cm after fixation The circumference of the stomach is 7 5 cm The mucosa of the duodenum is abnormal in appearance giving the impression of cobble stones There appeared to be about 12 rounded prominences on the surface of the duodenum, each varying from 4 to 8 mm in diameter and 2 to 3 mm in height In each instance the base

was broad Microscopically the soft projections were reported to be due to hyperplasia of the glands of Brunner There was no evidence of tumor formation

Following the operation the patient developed an anemia with the following comparison of pre- and postoperative blood counts

	12/10 47	12/19/47
RBC	5 070 000	2 620 000
HB	15 gm	7 gm

The cause of the anemia was not obvious since no great amount of blood was lost at operation and there was no postoperative melena Unfortunately no stool examinations for occult blood were recorded in the immediate post operative period On 12/25 47 the stool occult blood was negative

The postoperative fractional gastric analysis was done on 12/27/47 The fasting gastric contents titrated 107 units of free hydrochloric acid and 122 units of total acid The peak of 118 units of free hydrochloric acid and 136 units of total acid at sixty minutes seemed to represent a slight reduction from the preoperative figures

During the period following 12 21 47 the patient complained greatly of severe epigastric pain radiating to the back together with nausea and inter mittent vomiting The use of hourly feedings of milk and cream with antacid hourly on the half hour failed to control his symptoms A continuous intra nasal gastric drip was only partially successful in controlling his pain, and attempts to discontinue the drip were followed by increased severity of the pain

On December 29, 1947, an x ray examination of the operative site by barium meal showed a partial resection of the distal portion of the pylorus and the first portion of the duodenum with a Billroth No I type of anastomosis There were slight coarsening of the mucosal pattern of the stomach, and slight narrowing at the site of the ostomy with irregularity of the mucosal pattern just proximal to the ostomy as well as irregularity of the contour of the stomach These changes are considered to be postoperative in nature

The patient was discharged from the hospital on December 31, 1947 Be cause of continued symptoms the patient was readmitted to the hospital and a barium meal on January 12, 1948, showed a large ulceration proximal to anastomosis After failure of conservative measures a supradiaphragmatic vagotomy was done on January 17, 1948 Every effort was made to make this a complete vagotomy The esophagus was mobilized for a distance of 10 cm The two main vagi trunks and five to six additional strands were divided No strands could be palpated in the wall of the esophagus as it was lifted from its bed

An insulin tolerance test was done on 2/2/48 showing a fasting gastric acid of 120 units of free hydrochloric acid and 142 units of total acid The maxi- mum insulin effect on the blood sugar occurred at forty five minutes (blood sugar 38 mg per 100 cc), at which time the free acid was 57 units and total

acid 78 units The test was interpreted as indicating continued vagal influence on the gastric secretion in spite of the vagotomy

The patient s severe pain and intermittent vomiting persisted On March 4, 1948 reexamination of the operative site by barium meal confirmed the presence of a large defect interpreted as a marginal ulcer

On March 11, 1948 subtotal gastrectomy was performed by the author There was induration around the duodenum Dissection revealed a large ulcer crater at the posterior suture line, involving the pancreas The ulcer seemed more on the gastric than on the duodenal side of the suture line The ampulla of Vater was in the wall of the ulcer Bile squirted from the opening of the ampulla of Vater Conventional closure of the duodenum would have obstructed the common duct Therefore, the anterior wall of the duodenum was sutured to the base of the old ulcer crater in the pancreas A very high sub total gastric resection was done

Postoperatively the patient did well and was symptom free on March 31 1948, the date of discharge Roentgen examination of the operative site by barium meal on March 31, 1948, showed a well functioning gastrojejunostomy On March 17 1948, a specimen of fasting gastric juice showed no free hydrochloric acid and 50 units of total acid

On April 20, 1948, gastric analysis under controlled fluoroscopic guidance revealed a fasting acid of 31 units free hydrochloric acid and 42 units total acid A maximum acid value of 54 units free hydrochloric acid and 73 units total acid was reached at one hundred and five minutes

The patient was completely free of symptoms and able to return to work until September 1948 He then had another gastrointestinal hemorrhage as evidenced by melena and an anemia He was partially relieved by diet Dr Johnson and Dr Bockus decided that irradiation of the remaining portion of the stomach should be done This was done between November 6 and November 18 without a very appreciable effect on gastric acidity However, clinically he is well at this time (March 1949)

DISCUSSION

The marked hyperacidity without evidence of peptic ulcer plus the prompt development of a peptic ulcer after resection of the first and second portion of the duodenum causes one to speculate as to the relationship between the hyperacidity and the hypertrophy of Brunner s glands and the possible protection afforded by the secretion of these glands to peptic ulceration Experimental work as early as 1933 pointed to a possible protection to peptic ulceration by the secretion of these glands Floury and Harding studied isolated duodenal loops in many animals and found that the secretion from this loop was very high in bicarbonate content and that the secretion had some antipeptic activity The passage of hydrochloric acid over the duodenal mucosa stimulated the glands to secrete This was shown by an increase in the amount of secretion collected over a period of time, plus depletion in the mucin content of the glands if examined histologically

Mann and Williamson resected the entire duodenum and brought the

jejunum up and anastomosed it to the pyloric end of the stomach, anastomosing the ampulla of Vater the same distance from the pylorus as it was originally In two of ten animals, a definite peptic ulcer developed This lends further credence to the possible protective action of the secretion of Brunner s glands

This is not only of interest physiologically, but may have some practical significance because surgeons, as a rule, make no effort to save any part of the first or second portion of the duodenum The presence of the ampulla is the limiting factor in amount of duodenum resected In fact, because of the so-called trigger zone, some surgeons in order to be sure that all gastric mucosa is resected might remove more of the duodenum than is absolutely necessary

In conclusion, a case has been presented where apparently hypertrophied Brunner s glands afforded some protection against the digestive activities of a markedly hyperacid gastric secretion

PARTIAL GASTRECTOMY IN THE MANAGEMENT OF PEPTIC ULCER

L KRAEER FERGUSON, M D

INDICATIONS FOR SURGERY

In the treatment of peptic ulcer I believe that surgeons and gastroenterologists now see eye to eye, because the surgeons have arrived at the position where they recognize that the surgical treatment of ulcer should be reserved for those cases in which some of the complications of ulcer have appeared We recognize that medical therapy is of value and is the method of choice for the treatment of most uncomplicated ulcers With the appearance of complications surgical indications arise There is little argument concerning the necessity for operation in perforation and most medical men are of the opinion now that massive continuous hemorrhage from a proved ulcer, especially in the older age group, is most effectively treated by surgery Surgeons have become reconciled to the idea that most hemorrhages in younger individuals are medical problems

The change that has appeared in surgical thought has been with regard to the time at which surgical operations should be performed in cases of hemorrhage in the ages past forty five, whereas we used to treat these conservatively, we now are coming to the point where we believe that early operation, certainly operation before the patient goes into the irreversible stage, is the correct view

The third indication for surgery which is agreed upon both by the medical men and the surgeons is obstruction of the pylorus and of this indication we

have two types (1) the acute type which occurs as an acute inflammatory process associated with ulcer The inflammation may subside and the ob struction may be reversible, but in my experience these cases usually come to operation eventually (2) The cicatricial type that occurs in older individuals, where the cicatrix prevents reversibility and where surgery certainly has to be performed to relieve the pyloric obstruction

The fourth indication for operation in patients with ulcer is a broad and relatively indistinct one—an inability to control the ulcer by medical means Our lack of control or the lack of possibility of control by medical means in many cases means that the ulcer is complicated by posterior perforation into the pancreas or by other complications We are therefore treating the complications of ulcer But there are a few patients, the so-called intractable ulcer patients whose ulcer may not respond to medical care or the patient himself may be intractable to medical care In either case it appears that surgery offers him hope of relief

REVIEW OF HISTORY OF ULCER SURGERY

In considering surgery I think it is important for us to go back over the history of surgery for ulcer in order to understand the position to which we have come in the present day Some twenty to twenty five years ago we thought that the adequate operation for ulcer was a posterior gastroenterostomy We believed that the throwing of the alkaline juices of the upper intestinal tract into the stomach so neutralized the acid pepsin secretion that ulceration would heal This was true in a fairly large percentage of cases The difficulty was that not only did the alkaline juices of the upper jejunum enter the stomach but also the acid juices of the stomach entered the jejunum and the result was the appearance of marginal ulcers in a high percentage of cases

In the late 1920 s Dr Mann and Dr Williamson performed their classic experiment which showed that by diversion of the gastric acid ulcer could be produced wherever the intestine was anastomosed to the stomach This was an advance in that it showed us that the ulcer was produced by the acid pepsin mixture

More recent however and probably more important, is the work of Wangensteen and his associates A young man named Charles Code working in Wangensteen s laboratory on histamine intoxication devised a method of introducing histamine in beeswax subcutaneously to give off histamine over a long period of time In this experiment he noted the development of duo denal ulcer in all of his dogs This hypersecretion of acid pepsin induced by histamine was then used as a tool for the investigation of operative therapy of ulcer Wangensteen was able to show that a resection of 75 per cent of the stomach was the only operation which he had found regularly to prevent or to protect the resected animals against recurring ulcers

PHYSIOLOGY OF GASTRIC SECRETION

Now let us for a minute review the physiology of gastric secretion as a prelude to the question of operation for ulcer There are certain fundamental

principles of gastric physiology which have a great bearing on the success or failure of any operation carried out to cure and prevent the recurrence of peptic ulcers These facts are as follows First, the average duodenal ulcer patient secretes more gastric acid in response to stimulation than the normal person and what is perhaps more important, he secretes more gastric juice when no obvious stimulant is present Gastric secretion is stimulated in various ways The cephalic phase is mediated through the vagus nerves, it occurs as a result of subconscious cerebral stimuli associated with food and the emotions and is chiefly important when digestion is not in progress, even during sleep This is difficult to control medically

The gastric phase of gastric secretion is initiated by the mechanical distention of the gastric wall and by the chemical stimulation of food materials and the products of their digestion, delayed emptying of the stomach may prolong this phase and distention augments it The antral mucosa of the stomach is the source of an internal secretion, gastrin, which stimulates the acid secreting cells of the fundus Removal of the antrum decreases acid pepsin secretion *Failure to remove this area at operation is associated with a high incidence of recurrence in ulcer surgery* Most of the parietal cells which secrete acid and pepsin are in the fundus of the stomach These cells secrete *regardless of the source of stimulation To control satisfactorily the important* acid pepsin factor one should attack the source of the secretion, rather than the individual sources of stimulation such as the vagus nerves Complete vagotomy, *for example, will not protect the dog from* ulcer produced by histamine stimulation of gastric secretion

The mucous membrane of the small intestine becomes more vulnerable to the action of acid and pepsin as you pass downward from the pylorus This was demonstrated also by Wangensteen who showed that the further down the anastomosis was made on the jejunum, the more probable was the development of a recurrent ulcer

TECHNIC OF SUBTOTAL GASTRIC RESECTION

In consideration of these facts in clinical experience it is our opinion that subtotal gastric resection properly planned and executed is the best surgical approach to the ulcer diathesis The resection should remove enough of the secreting area of the gastric wall to control *effectively the acid pepsin factor* during any and all stages of gastric secretion The pylorus and ulcer bearing portion of the duodenum should be removed when this is technically safe *When the antral portion of the stomach cannot be removed* its mucous membrane should be stripped off and removed to eliminate its humoral influence on gastric secretion The end of the resected stomach should be anastomosed *to the* jejunum as close to the ligament of Treitz as possible since this area is less vulnerable to recurrent ulceration There should be no delay in gastric emptying We have attempted to satisfy these criteria by using a modification of the Hofmeister-Polya subtotal gastric resection Approximately 75 per cent of the stomach is removed, comprising practically all of the lesser curvature

and the greater curvature up to the vasa brevia including most of the branches of the left gastroepiploic artery (Fig 108)

Gastrointestinal continuity is restored as close to the ligament of Treitz as possible I might add a word or two about the technic here because it is interesting if not important to medical men The difference between an anterior and a posterior operation, of course, is the position of the colon Wangensteen feels that a posterior operation is made closer to the ligament of Treitz than is an anterior operation and that this is of value On the other hand, if we have recurrent ulcer, the posterior operation greatly increases the difficulty in taking care of the lesion The posterior anastomosis increases the

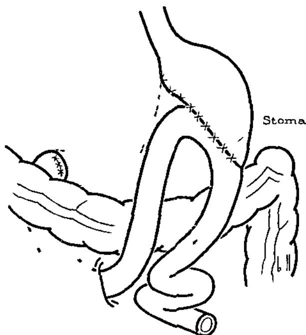


Fig 108 Hofmeister Polya resection for peptic ulcer The gastrojejunostomy is made anterior to the colon and the distal jejunal loop is at the greater curvature The infolding of the remnant of lesser curvature forms a baffle to direct the gastric flow to the efferent jejunum

likelihood of development of a gastrojejunocolic fistula if a jejunal ulcer should occur And the distance between the ligament of Treitz and the anastomosis in an anterior operation is not more than 1 inch greater than that in a posterior operation We prefer to work without clamps because we believe we can do a higher resection with less difficulty The entire lesser curvature is removed as a rule A radical resection without this high a resection of the lesser curvature is impossible

There is one other technical point that I think is important in consideration of this type of operation and that is whether the stoma should be made to include the entire cut end of the stomach or only part of it We prefer the

so-called Hofmeister type of operation with anastomosis of the distal loop to the greater curvature, because the Hofmeister infolding of the lesser curva ture produces a sort of a baffle which more or less directs the flow of gastric contents into the efferent loop A review of the postoperative x rays of these cases has shown that a relatively small amount of barium enters the proximal loop when the operation is performed according to this method

RESULTS IN SUBTOTAL GASTRIC RESECTION

The mortality risk is less than that of the disease for which the operation is performed Furthermore it offers the patient not only relief from pain, but relief from much of the monotony of dietary restriction as well Rarely in our experience has it imposed significant difficulties in the patient Wangensteen has shown that this type of operation will protect against the ulcer regularly provoked by histamine in the dog He has carried this into clinical practice and recently reported a series of 500 consecutive patients resected in essentially this way for ulcer In this group there were two marginal ulcers that developed after operation, in both instances the resections were not high enough Further resection at the proposed level effected a satisfactory result in each case The results of more conservative resections suggest their in adequacy

In 1945 Rienhoff reported his results following 260 consecutive resections that included approximately half of the gastric wall There was proved or strongly suggestive evidence of marginal ulceration in 21 per cent It is this type of resection that is responsible for the statement that gastric resection offers no more protection against recurrence than does gastrojejunostomy

Our experience with liberal resection has closely paralleled that of Wangen steen In over 200 resections performed there were only 6 instances of proved or suspected marginal ulceration In each instance it was obvious that the primary operation was inadequate according to the criteria we have indicated The results recorded by Gardner and Hart at Duke are some of the latest follow-up reports They report, following partial resection, 84 per cent en tirely relieved, 5 per cent not completely relieved, 5 per cent recurrences Other clinics report comparable results

OPERATIVE MORTALITY

The operative mortality for elective gastric resection is now remarkably low In the larger clinics of this country it varies from 1 to 3 per cent Reviewing some of these statistics, Grove at Emory University reported 1 death in 150 cases—0 66 per cent, Gardner and Hart at Duke University reported 123 cases with 10 deaths or a mortality of 8 9 per cent which is a relatively high one Throughout the country the mortality from radical resection for ulcer has been somewhere in the neighborhood of 1 to 3 per cent In our own series the mortality was 2 per cent In 100 consecutive cases there were no deaths

POSTOPERATIVE SEQUELAE

We have not been impressed by the fact that removal of 75 per cent of the stomach imposed significant new difficulties on the patient Occasionally undesirable sequelae appear but these rarely interfere with the patient s ability to work and are never so disabling as the disease for which the operation was undertaken There have been those who fail to gain weight after resection, a number have complained of nausea on arising for some months, a few have symptoms suggesting transient hypoglycemia after eating This is usually of short duration There have been no profound or incapacitating dumping syndromes in this series There are a few cases following high resection in which some adjustment has to be made This is usually made by the patient himself and it occurs due to the dilatation of the gastric stump The patient unable to eat an ordinary meal is necessarily forced to take frequent small feedings at first but after a relatively short time, a period of something like four to six weeks, these patients gradually become able to eat normal meals without the feeling of fullness and distention which they had at first

COMMENT

An adequately performed partial gastrectomy has now become established as a safe and effective method and one which does not subject the patient to a very marked disability We are therefore at the present time unwilling to discard an operation that carries such a prospect of precluding recurrent ulceration It is hoped that some method of achieving the same result by more conservative means may some day be found

EXPERIENCE WITH THE DUMPING SYNDROME

THOMAS E MACHELLA, M D

One of the functions of the stomach is that of a reservoir Normally it evacuates a mixed meal in about three to four hours at an estimated rate of about 10 to 15 cc per minute When the gastrointestinal tract has been deprived of its gastric reservoir as after a gastroenterostomy or a subtotal gastric resection the ingested food may enter the jejunum almost immediately and give rise to unpleasant symptoms These constitute what has been called the dumping syndrome

The symptoms consist of any combination or all of the following a feeling of warmth sweating tightness or pain in the epigastrium, nausea, weakness palpitation vertigo or even collapse They vary in severity and in the degree to which they incapacitate the patient but usually cause him to lie down after meals until they subside They occur after all meals in some individuals, or only after certain ones in others They usually make their first appearance

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Our experience with liberal resection has closely paralleled that of Wangensteen In over 200 resections performed there were only 6 instances of proved or suspected marginal ulceration In each instance it was obvious that the primary operation was inadequate according to the criteria we have indicated The results recorded by Gardner and Hart at Duke are some of the latest follow-up reports They report, following partial resection, 84 per cent entirely relieved, 5 per cent not completely relieved, 5 per cent recurrences Other clinics report comparable results

OPERATIVE MORTALITY

The operative mortality for elective gastric resection is now remarkably low In the larger clinics of this country it varies from 1 to 3 per cent Reviewing some of these statistics, Grove at Emory University reported 1 death in 150 cases—0 66 per cent, Gardner and Hart at Duke University reported 123 cases with 10 deaths or a mortality of 8 9 per cent which is a relatively high one Throughout the country the mortality from radical resection for ulcer has been somewhere in the neighborhood of 1 to 3 per cent In our own series the mortality was 2 per cent In 100 consecutive cases there were no deaths

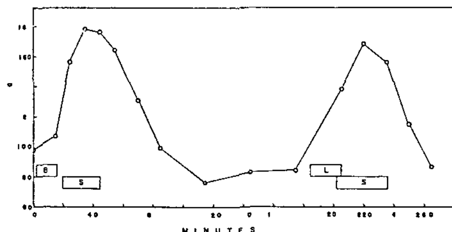


Fig 110 Blood sugar curves after breakfast (B) and lunch (L) The dumping symptoms (S) appeared shortly after breakfast was completed and again after lunch

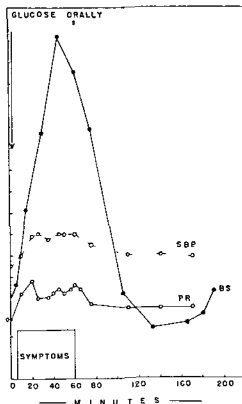


Fig 111 Blood sugar curve after oral administration of glucose Severe dumping symptoms occurred and were associated with an increase in pulse rate (P R) and systolic (S B P) and diastolic blood pressures In this and subsequent figures the ordinates represent blood sugar in mg % pulse rate per minute and blood pressure in mm mercury

when the patient resumes feedings postoperatively and may trouble him for weeks to years Some learn that the avoidance of certain foods or of liquids may result in the failure of the "dumping" symptoms to develop

The mechanism of production of the symptoms has been variously ascribed It has been maintained that the symptoms are due to hyperglycemia (hyperglycemic shock) as a result of rapid absorption of carbohydrate from the jejunum It has also been held that they are due to hypoglycemia which occurs after and secondary to the hyperglycemia An entirely different explanation is that the symptoms result from mechanical distention of the jejunum by the 'dumping' of food into it It has also been stated that there are two sets of symptoms (1) early postprandial, due to mechanical distention of the jejunum by *the ingested food, and (2) late postprandial, due to hypoglycemia*

In view of the above conflicting opinions as to the mechanism of production of symptoms and the time of their occurrence in relation to the ingestion of a meal, a number of experiments were performed on 16 post partial gastrectomy patients manifesting dumping symptoms and on control subjects with intact stomachs As a result, a mechanism for the development of the early postprandial symptoms has suggested itself which appears to explain the clinical and experimental observations more satisfactorily than any of the other previously proposed ones

RESULTS

1 *Time of Occurrence of Symptoms in Relation to Ingestion of a Meal* The symptoms occurred toward the end of a meal (Fig 109) or almost immediately

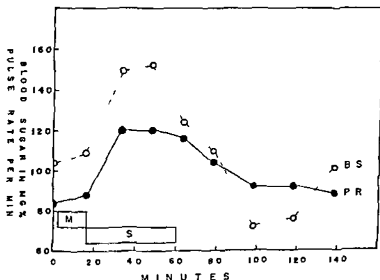


Fig 109 Blood sugar curve (B S) following ingestion of a mixed meal (M) The dumping symptoms (S) appeared just as the meal was completed and were accompanied by an increase in pulse rate (P R) and blood pressure

after its completion and were associated with an increase in pulse rate and blood pressure

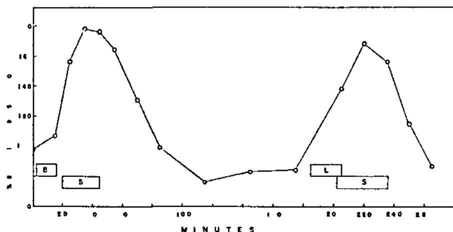


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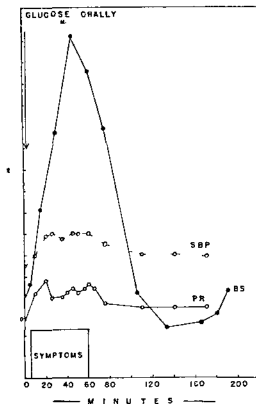


Fig 111 Blood sugar curve after oral administration of glucose Severe dumping symptoms occurred and were associated with an increase in pulse rate (P R) and systolic (S B P) and diastolic blood pressures In this and subsequent figures the ordinates represent blood sugar in mg % pulse rate per minute and blood pressure in mm mercury

2 *Relation of Time of Occurrence of Symptoms to Blood Sugar Concentration* A *Following a Mixed Meal* After a mixed meal, the symptoms occurred during the period of hyperglycemia and began to abate as the blood sugar fell (Fig 110) The symptoms reappeared after the ingestion of a second meal It is well to keep in mind these blood sugar curves when one encounters a positive test for sugar in the urine in postgastrectomy cases

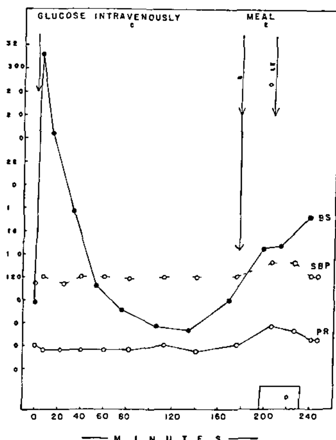


Fig 112 Blood sugar curve after injection of glucose intravenously No symptoms or signs of the dumping syndrome occurred despite the fact that the blood sugar levels attained were as great as those following oral administration of glucose (see Fig 111) The symptoms did occur however when a mixed meal was administered subsequently

B *Following Oral Administration of Glucose or Sucrose* Shortly after the ingestion of *100* gm *of glucose or sucrose in 250 cc of tap water unusually* severe "dumping symptoms appeared and persisted during the period of hyperglycemia (Fig 111) The symptoms were always more severe than those observed following mixed meals

3 *Comparison of Effects of Glucose Administered Orally and Intravenously* The injection of 0 5 gm kg of glucose intravenously in form of 50 per cent solution was not followed by the development of symptoms or signs of the

dumping syndrome despite the fact that the blood sugar levels attained were as great as those following oral administration of glucose (Fig 112) An elevation in blood pressure or an increase in pulse rate likewise did not occur The symptoms did, however, occur after a mixed meal was ingested subsequently

4 *Effect of Instillation of Hypertonic Glucose Solution into an Isolated Segment of Intestine* The jejunum of a normal young healthy adult male (stomach intact) was intubated with a double lumen Miller-Abbott tube, one lumen of which was connected to a balloon, the other arranged to deliver a solution of hypertonic glucose into a section of the jejunum proximal to the balloon

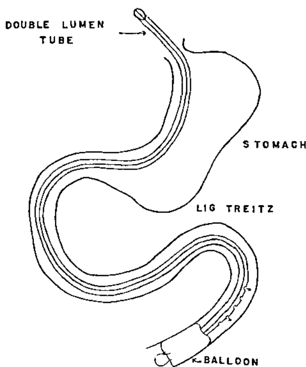


Fig 113 Diagram of intubation arrangement used for obtaining data in Fig 114

(Fig 113) The balloon was inflated with sufficient air to obturate the lumen but not produce manifestations of gut distention Then 250 cc of a solution containing 100 gm of glucose was introduced into the isolated segment of jejunum Almost immediately after the solution had entered (Fig 114) the patient broke out into a sweat experienced nausea and became pale The pulse rate and blood pressure increased and he made an unsuccessful effort to withdraw the tube The balloon was quickly deflated with a prompt lessening in severity of the symptoms They persisted however in milder degree for about fifty minutes NOTE *The symptoms were greatest in intensity before the hyperglycemia developed and the balloon was deflated*

5 *Volume of Fluid Aspirated from an Isolated Loop of Intestine Following Instillation of Hypertonic Solutions* By means of an intubation technic used for studying absorption from an isolated segment of intact intestine, 30 cc of a saturated solution of sodium sulfate was introduced into the upper intestine Continuous aspiration, at a point 75 cm below the area into which the solution was introduced, yielded a volume of solution six to eight times that introduced This occurred at a rate of 8 0 cc per minute as compared to an average rate of flow of 0 8 cc before the sodium sulfate was instilled A similar increase in volume of a glucose solution introduced into the gut was reported in 1937 by Abbott, Karr and Miller They found that the volume aspirated

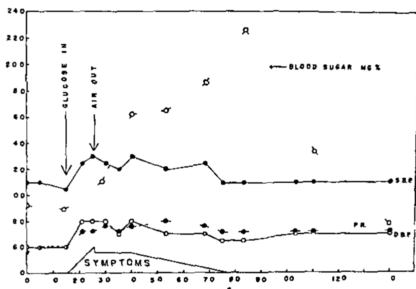


Fig 114 The production of dumping symptoms in a normal subject by the instillation of 100 grams of glucose in 250 cc water into a balloon isolated section of jejunum The symptoms were of such severity that the balloon had to be deflated They appeared before the blood sugar concentration increased sufficiently to be termed a hyperglycemia and were accompanied by an increase in pulse rate (P R) and systolic (S B P) and diastolic (D B P) blood pressures The manifestations of dumping syndrome persisted in less severe degree however for about fifty minutes after the balloon was deflated

was directly proportional to the concentration of glucose introduced Dr Ravdin and his associates found a similar situation to hold true for the stomach

6 *Effect of Distending the Intestine by an Air-Inflated Balloon* Distention of the efferent jejunal loop by an air inflated balloon immediately was followed by pain in the epigastrium palpitation, sweating weakness and an increase in blood pressure (Fig 115) The severity of the symptoms was directly proportional to the degree of distention The symptoms and circulatory changes promptly abated when the balloon was deflated Reinflation reproduced the symptoms

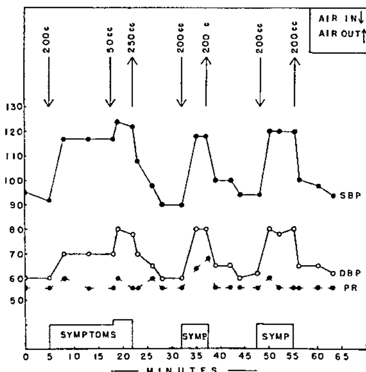


Fig 115 The reproduction of the manifestations of the dumping syndrome by balloon distention of the efferent jejunal loop Deflation of the balloon caused the symptoms to disappear and the blood pressure to return to normal levels

COMMENT

On the basis of the experiments described and the reported data of others, the following explanation of the mechanism of production of the early post prandial dumping symptoms seems likely The symptoms are caused by distention of the jejunum this distention is caused by the fluid which enters the gut from the blood stream in an attempt to dilute a hypertonic solution resulting when various foodstuffs possessing osmotic properties are eaten

In support of the proposed mechanism are the following clinical and ex perimental observations

1 *The symptoms occur toward the end of or shortly after the completion of a meal* at which time a hypertonic solution is first made available to the jejunum for dilution

2 *The absence of any consistent correlation between symptoms and blood sugar concentration* Despite the fact that a hyperglycemia may be demonstrated during the period of symptoms induced by the ingestion of a mixed meal or of a sucrose or glucose solution one should not ascribe the production of symptoms to the hyperglycemia for several reasons

(a) Dumping" symptoms do not occur when the hyperglycemia is induced

by the intravenous injection of glucose in subjects with the dumping syndrome

(b) 'Dumping symptoms can be demonstrated to occur before hypergly cemia occurs as a result of intrajejunal instillation of glucose solution

(c) The blood sugar concentration may rise to considerable height after a meal in a gastrectomized patient and yet no 'dumping' symptoms occur if the meal or glucose solution gives rise to diarrhea

(d) "Dumping symptoms may be produced by the instillation into the intestine of hypertonic solutions of magnesium and sodium sulfate, which do not produce a hyperglycemia They may also occur after the instillation of concentrated protein hydrolysate solutions if diarrhea does not result

3 *The third line of evidence in favor of the mechanical distention idea is that the "dumping symptoms can be reproduced by balloon distention of the intestine* However, that it is not the distention by the volume of the ingested food itself is indicated by the fact that meals or liquids of equivalent bulk are not always followed by dumping symptoms To produce symptoms, the meal should possess several characteristics and certain conditions must be present

(a) Ingredients capable of exerting osmotic pressure must be present in the meal The ingredients are usually sugars, but can be electrolytes and protein products

(b) Enough fluid must be ingested during the meal to dissolve the ingredi *ents possessing osmotic properties and yet form a hypertonic solution* of sufficient strength to draw additional fluid from the blood stream into the gut

(c) Fluid must be readily mobilized from the blood stream to enter the gut lumen with sufficient rapidity to distend it That such fluid does enter the intestine in response to the presence of a hypertonic solution is evidenced by the ability to aspirate several times the volume of a hypertonic solution intro duced into an isolated segment of intestine within a short time of its entry

(d) The energy expended by the diluting mechanism in distending the lumen must not be dissipated by vomiting or by the production of such excessive hyperactive propulsive peristalsis that the meal is dispersed rapidly throughout the small intestine In some of our cases this was so marked as to give rise to diarrhea It has been demonstrated by Abbott, Karr and Miller (1937), employing roentgenologic, balloon-kymographic and chemical analytic methods, that the propulsive activity of the small intestine increased directly as the concentration of glucose introduced

MANAGEMENT OF PATIENTS WITH THE DUMPING SYNDROME

We employ two measures for the prevention of symptoms in individuals with the dumping syndrome, i e , the early postprandial symptoms

1 The patient eats only nonliquid food materials during the meal Fluids are taken between meals

2 If he wishes to eat a full course meal (as when invited out, etc), he takes atropine, 1/50 to 1/100 grain, about one-half hour before the meal and takes

a chance on not being able to use his eyes for close work for a while thereafter (Fig 116)

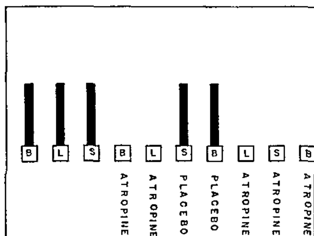


Fig 116 The effect of atropine (1/75 gr) administered orally one half hour before breakfast (B) lunch (L) and supper (S) on successive days The dumping symptoms (dark columns) occurred when nothing or a placebo was administered before meals but did not occur when atropine was given

SUMMARY

It may be said that the symptoms comprising the dumping syndrome are sometimes encountered in individuals who have a rapid entry of ingested food into the jejunum as after a gastroenterostomy or subtotal gastric resection with a large stoma The mechanism thought to be responsible and methods of overcoming it have been described

Dumping symptoms, however can be encountered in other individuals and occasions

1 Following instillation of magnesium sulfate into the duodenum for the purpose of evacuating the gallbladder

2 In individuals who are being fed by stomach tube if the tube happens to slip into the duodenum

3 In patients receiving intrajejunal alimentation if the material enters too rapidly and

4 Occasionally after a heavy meal in individuals with very rapid gastric emptying time

Finally, it will be well to keep in mind the possibility of postprandial hyperglycemia and glycosuria in postgastrectomy nondiabetic individuals

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purely mechanical, since belching is commonplace after many of the soluble alkalis and relief of distress follows soon after this occurs

I do not advocate the use of amino acids as antacids I fully agree they have an important place to play as a means of fortifying protein intake, particularly in the protein deficient diets fed so often to patients with active gastroduodenal ulcer However, I personally employ hydrolyzed protein only rarely in the management of uncomplicated ulcer I know of no convincing evidence that the patient with an uncomplicated ulcer requires hydrolyzed protein and cannot digest whole protein I fortify protein intake in these patients by giving them simple skim milk powder and I would not hesitate to recommend this preparation

DR BOCKUS You prefer skim milk powder for economic reasons?

DR BERK I do it for economic reasons as well as for palatability

Question Dr Schoen have you made any studies relative to the effect of vagotomy on pancreatic secretions?

DR SCHOEN No I have not

DR BOCKUS Would you like to hear either from Dr Friedman or Dr Thomas both of whom have? Who would like to answer that, Dr Friedman or Dr Thomas?

DR THOMAS I know of only two studies that have been made Dr Crider and I, some years ago, studied the effect of vagotomy on the response of the pancreas to peptones soap, and hydrochloric acid in the intestine and the results showed that while immediately after vagotomy there was no response to peptone the response did in time return to about 60 per cent of its normal value The response to soap was not affected at all but the response to hydrochloric acid, surprisingly was reduced just as much as the response to peptone

A later study by Dr Pincus has shown that the response to meals that is pancreatic secretion formed during the digestion of an ordinary meal, is reduced somewhere between 60 and 80 per cent after vagotomy The effect here no doubt is in part due to the delayed gastric emptying

Question What effect does vagotomy have on the motility of the digestive tract—i e the small and large intestine?

DR MACHELLA Most of the studies of small intestinal motility following vagotomy have revealed no changes which could be attributed to the effect of the vagotomy on the small intestine itself Dr Shiffer, of our Department of Radiology, observed after vagotomy a greatly delayed transit time for barium from the pylorus to the cecum He felt that this delayed transit time was largely due to the very poor emptying of the stomach Motor disturbances theoretically need not necessarily occur following vagotomy if it is true that the three main motor activities of the small intestine i e rhythmic segmentation peristalsis and pendular movements have their origin in myogenic and intrinsic nervous mechanisms Section of the vagi could however, remove any additional influence transmitted through them to Auerbach s plexus such

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PANEL DISCUSSION

Question Dr Willard, what is the protein content in grams of the usual Sippy type diet regimen that you employ?

DR WILLARD The average Sippy type program utilizes between a quart and half and two quarts of milk daily, depending on the amount used per feeding That would provide a protein content of somewhere between 50 and 70 gm unless it is reinforced with some type of protein concentrate or amino acid preparation

DR BOCKUS Do you advocate some protein reinforcement, Dr Willard?

DR WILLARD I think these patients, particularly those who have had pro longed symptoms and have been on a restricted diet for any period of time, or those who have been losing weight, should be given some dietary addition *of protein concentrate, or possibly hydrolysate*

Question Since it has not been shown that there is an unequivocal re lationship between hyperacidity and ulcer symptoms—ulcer recurrence—what is the rationale of the use of antacids? Why use amino acids for this purpose alone in contradistinction to their protein value per se?

DR BERK An impressively large number of substances have been cate gorized as antacids Some are soluble alkalis, some are insoluble gels, some are chemically reactive, others show no chemical reaction Yet, the basic action ascribed to all of them is reduction of gastric acidity and the relief of symptoms following their exhibition is attributed to reduction in acidity However, the precise role of acid in the production of pain in ulcer is still under investigation All of us have witnessed relief of heartburn and upper abdominal distress after antacid ingestion by individuals with pernicious anemia and true anacidity Certainly reduction in acidity would not appear to be the mechanism responsible for relief in such cases There is reason to think that many of the symptoms for which antacids are prescribed may result from hypertonicity Such hypertonicity or other upper gastrointestinal motility derangements may be relieved by antacids because of direct action by them on the neuromuscular apparatus In some cases the changes may be

DR FRIEDMAN I ve had no experience with the use of detergents to increase fat absorption The report from Boston has shown that Tween 80 will increase fat absorption We have recently been using Tween 80 together with the fat soluble vitamins in children I don t know what the results will show—it was just started several days ago There s one thought that enters my mind Tween 80 is in itself a substance that will destroy or inactivate some of the enzymes I don t know how one can reconcile the use of detergents for fat absorption with their effect in inactivating digestive enzymes

DR BOCKUS Do you think we have sufficient proof from the work that has been published up to this time to indicate that these substances actually do increase the absorption of fat through the intestinal wall?

DR FRIEDMAN I think the evidence at the moment is only presumptive As a matter of fact, the absorption—if it is shown to be increased—may not necessarily be due to the effect of the detergent on the mucosal surface, but as Dr Waldron at our place thinks, it may very well be due to its effect on altering the intestinal motility

DR BOCKUS A question for Dr Ferguson Do the mortality figures for partial gastrectomy rise appreciably with removal of the ulcer bearing area of the duodenum?

DR FERGUSON That s a question that s hard to answer There s no question but that the operation becomes more difficult as it extends downward on the duodenum, and especially if there are posterior ulcers or perforating ulcers in that area Nevertheless, it is usually possible to remove the ulcer-bearing area in all but those with an inflammatory ulcer Occasionally, cases are encountered in which scarring has so greatly altered the area that it is difficult to excise the ulcer In such cases it is perhaps wiser to operate conservatively by dividing the stomach, removing the mucosa of the antrum down to the pylorus, inverting the distal gastric wall and then doing the resection In the cases that I reported something over 100, without a death, the ulcer bearing area of the duodenum was removed in all but three patients, I believe, so that this procedure is not too dangerous

Question Aren t all surgeons agreed (you can make a speech on this for hours, but I hope you won t) that ulcer perforation is an absolute indication for surgery? Would Dr Ferguson comment on the merit of the conservative management recently recommended i e , decompression of the stomach intravenous fluids, etc , rather than operation?

DR FERGUSON In the last four or five years, there have been some who have recommended that perforated ulcer should be treated by intubation That is intubation of the stomach with aspiration of gastric contents intra venous fluids and conservative therapy There have been several reports from England and in this country also several reports have appeared Now the fact that you can save the life of a patient who has had a perforated ulcer by this means by no means recommends it as a method of therapy We all know that when ulcers perforate, they may become adherent to the under surface of the liver, or become sealed off by the omentum and in this way further

as have been thought to be responsible for the small intestinal hypermotility sometimes seen in association with duodenal ulcer We observed a temporary adynamic ileus in one patient and a more prolonged dilatation of the small intestine in another

Roentgen observations on the appearance of the colon of our patients, made before and after vagotomy, are in agreement with those of Grimson et al (1947) They observed no definite abnormalities in the appearance of the colon visualized twenty-four hours after the ingestion of barium or by barium enema

Question Does urecholine always work on a vagotomized retentive stomach?

DR. MACHELLA It works provided the dose is large enough and there is no obstruction at the outlet of the stomach The drug, when administered orally must get into the intestine to be absorbed One should always determine beforehand whether or not an injection of the drug will evacuate a barium filled stomach

Question Are urecholine and doryl on the market? Who makes them?

DR MACHELLA Urecholine and doryl are both on the market now They are made by Merck & Company

DR BOCKUS Another question concerns the occurrence, prevention and management of ulcer in the sympathectomized patient? Would you mind answering that question, Dr Machella?

DR MACHELLA I must confess I ve had no experience with this sort of situation There has been a case reported in the J A M A (*133* 1207, 1947), where it was suggested that a gastric ulcer was aggravated following dorso lumbar sympathectomy Another patient, referred to in the same article, had both a vagotomy and a sympathectomy performed He died shortly after from peritonitis secondary to perforated duodenal ulcer I would watch, very carefully and closely, a peptic ulcer patient who was subjected to sympathectomy, not only because of the theoretical possibilities that the ulcer might be adversely influenced, but also because the danger signal of penetration and threatening perforation (pain) might no longer be evident after sympathectomy

DR BOCKUS In a patient with hypertension, would you recommend a sympathectomy if the same individual had duodenal ulcer disease?

DR MACHELLA The decision would have to be individualized and the risks carefully considered I think I would not hesitate to recommend sympathectomy if, after carefully studying and evaluating the patient, I could assure myself that he would be capable of and willing to adhere to a very, very strict medical ulcer regimen Such a patient would have to be supervised very closely

Question Discuss the use of detergents after gastric resection to increase fat absorption and prevent steatorrhea

quately performed partial gastrectomy It happens to be my viewpoint that in the complicated ulcer requiring surgery at the present time I prefer partial gastrectomy In my own experience, during the last few years, we have had not more than 5 per cent recurrences following this operation Perhaps at the end of three or four years I may change my views concerning the combined operation It is now being done in a number of clinics We should know after four or five years what the end results are

Finally, I am sorry if I gave any of you the impression that I was unfair, I was merely giving you my opinion concerning the obvious failure of vagotomy alone in the treatment of gastric and duodenal ulcer requiring surgery It happens that most conservative surgeons and most internists with a large experience agree today with the views that I have expressed

contamination of the peritoneal cavity may be avoided The possibility of saving the patient's life by intubation rests on the hope that somehow the ulcer may close It seems to me that with surgical closure of the perforation, *the mortality is so low, the results are so good, and the treatment is so direct* that the universal adoption of conservative therapy is exposing the patient to a big risk I wouldn t want to take it and I don t think any of you would want to take it

Now, is there no place for intubation and aspiration and intravenous fluids in the management of ulcer perforation? Yes, I think there is Many patients who have gone beyond the time when surgery can be of benefit, when surgery is even dangerous, have to be treated this way We have had 5 or 6 such patients, and I must say that some of them have lived One of them lived with a perforated gastric ulcer and a pseudo-diverticulum of his stomach involving the whole inner surface of his diaphragm and down to his mid abdomen, all connecting with his stomach Nevertheless I do not think that intubation is the logical way to treat a perforation of the intestinal tract

Dr Bockus The hour is getting very late and I cannot detain you much longer It s impossible to answer all of the questions which have been sub mitted I think I will have to end the panel myself because of a criticism which I find here of my discussion of vagotomy

Question 'Don't you feel it is unfair to give this gathering so one sided a picture of vagotomy? ' Are there not many eminent and honorable internists and surgeons who favor vagotomy for properly selected patients and whose opinion is worthy of consideration?

Dr Bockus If I gave the impression that everyone who disagreed with me is dishonorable, and not eminent, I would like to withdraw my comments, but when I discuss a subject before a group of this type, I have made it a policy to be frank I presume that you want my opinion Now there are those who differ, but the differences as time goes on, which I tried to point out, are gradually being ironed out

I have just come from a meeting in another city where I sat around the table with 10 of the leading gastrointestinal internists in this country, with a sprinkling of two or three physiologists There was not anyone at that gather ing that would disagree with anything I have said about vagotomy here this morning The most radical exponents of *vagotomy alone*, as I told you, are no longer doing vagotomy alone They themselves agree that simple vagot omy, except in a few instances that we mentioned, had better be discarded

The only criticism here, then, would be whether or not we re justified in going on with a prolonged experiment of vagotomy plus these other opera tions My mind is open about them There is another question here that re minds me that in a certain clinic in this country over 200 patients had been operated upon with vagotomy, plus gastroenterostomy and pyloroplasty I have reviewed their most recent report and it doesn t change my mind We will not be able to decide whether or not this combination of vagotomy with gastroenterostomy or pyloroplasty will prove superior or inferior to the ade

Application of Neuropsychiatry to Gastrointestinal Problems

EXPERIMENTAL OBSERVATIONS ON CHANGES IN EMOTIONAL STATE AND PHYSIOLOGIC DISTURBANCES IN THE GASTROINTESTINAL TRACT

STEWART WOLF, M D

It gives me a great deal of pleasure to participate again in this session of the American College of Physicians Because the assignment of Dr Bockus binds me to cover the experimental evidence of physiologic disturbances in the whole gastrointestinal tract, I ll have to omit details and offer samples of the data from each level

These experimental observations have been made in collaboration with a large group of workers in our laboratory at Cornell-New York Hospital, including Drs Morton Bogdonoff Thomas P Almy, William J Grace and Harold G Wolff

MOUTH

Concerning salivary changes which have always interested those experimental physiologists who have been aware of psychosomatic phenomenology

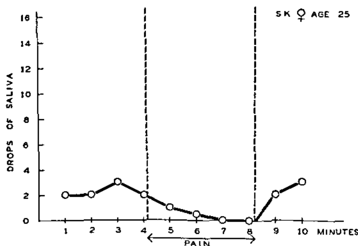


Fig 117 Rate of salivary flow from left parotid duct before during and after the tooth drilling Reaction of hypofunction

our observations are fragmentary and derived from experiments done in the dentist s chair Continuous collections of saliva were made from Stensen s



Fig. 119 Characteristic x ray appearance of the barium filled esophagus in cardiospasm. Note diffuse dilatation and sigmoid deformity at the lower end

















Fig. 120 Experimental observations on the time required for swallowed barium to reach stomach from the esophagus Each circle represents an hour and the blackened portion the length of time the barium remained in the esophagus Saw tooth edges indicate conclusion of the period of observation while barium was still in the esophagus

relationship with his children. He realized that he favored a daughter at the expense of his son. He reiterated regretfully, "I wish I could like him but he's so much like me." Eventually it was possible for him to reorient his

duct on one side in a group of 24 individuals Measurements of salivary flow were made prior to drilling by the dentist, during drilling, and following the end of the drilling period Drilling was not an invariably painful experience but it was invariably a distasteful one In this group of patients 6 reacted to

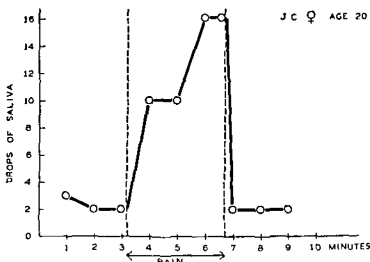


Fig 118 Rate of salivary flow from left parotid duct before during and after the tooth drilling Reaction of hyperfunction

the stress with diminution in salivary output as shown in Fig 117 Seventeen reacted with a pronounced increase in salivary output during the drilling experience (Fig 118) and one easy-going elderly man showed no significant change

ESOPHAGUS

CARDIOSPASM AND ESOPHAGEAL HYPERMOTILITY

The association of symptoms of cardiospasm with periods of stress is familiar to clinicians In Fig 119 is shown the x ray of an individual with well developed cardiospasm The esophagus is dilated and S-shaped Experimental procedures were carried out on 14 such individuals with greater or lesser degrees of cardiospasm Each one was repeatedly given a measured amount of barium, 30 cc of a standard consistency, to swallow The length of time required after swallowing to pass from mouth to stomach was recorded

Figure 120 illustrates the results of several such observations on the subject whose esophagus is pictured in Fig 119 Each circle represents an hour and the blackened part of the circle represents the length of time it took the swallowed barium to pass from mouth to stomach The saw tooth edges indicate that the passage took longer than the period of time indicated, but that the experiment was terminated at that time In this individual, on repeated occasions more than fifteen minutes were required for the swallow of barium to reach the stomach The subject was in conflict as regards his

a noxious substance which has been swallowed or perhaps a protection against someone trying to shove something down his throat



Fig 122 Delay in esophageal emptying induced in a normal subject by the ingestion of extremely cold and extremely hot barium

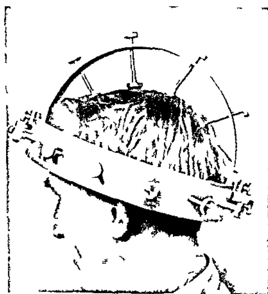


Fig 123 Metal crown used to induce head pain

An attempt to test this notion and to determine whether or not other threats to the organism s integrity, not directed at the gastrointestinal tract

attitude toward the boy and achieve a somewhat more constructive relationship in the family Following this, he repeatedly emptied his tortuous, widely dilated esophagus in less than thirty seconds

Figure 121 illustrates a short experimental situation in another patient with cardiospasm and a dilated esophagus During relative relaxation this forty-six year old woman's swallowing time was less than thirty seconds During a discussion of her husband, however, it was lengthened to fifteen minutes Associated with the obstruction in this individual and in most of the subjects observed there was marked hypermotility in the esophagus Except in those with extreme dilatation, the lower two-thirds of the esophagus displayed predictable hypermotility during the period of greatest delay in emptying Frequently, the spasm would cause the barium to shoot upwards above the arch of the aorta so that it was occasionally regurgitated back into the mouth Often the irregular contractions caused it to travel up and down the esophagus like a water hammer



Fig 121 Prolongation of swallowing time in a subject with cardiospasm during a discussion of relevant personal conflicts

Figure 122 illustrates an attempt to induce the picture of cardiospasm artificially in a normal twenty-six year old girl by applying noxious stimuli to the esophagus Like the other normal subjects whom we studied, the swallowing time of this individual was less than twelve seconds After establishing a base line she was given very hot barium to swallow at 63° C The barium remained in her esophagus for more than a minute The column of barium was pinched off at the lower end and hypermotility was readily noted A subsequent swallow of very cold barium at 6° C likewise was delayed in passage through the esophagus The x-ray illustrated in Fig 122 was taken at the end of two minutes The same phenomenon was later provoked in this subject by causing her to swallow barium mixed with tabasco sauce After a rest period from these procedures her swallowing time as tested with the ordinary barium mixture was again less than twelve seconds

Comment These findings suggest that the biologic response of cardiospasm may represent an attempt of the human organism to defend its stomach from

which touched the patient more deeply than did the physical traumata Before the Neurology examination the swallowing time lengthened to three minutes and a quarter Following the examination it returned to ten seconds Two of the 11 subjects showed such evidence of cardiospasm before examinations

STEPS IN THE DEVELOPMENT OF CLINICAL CARDIOSPASM

Figure 125 illustrates a chain of events observed in a patient whose x rays, taken before symptoms had become well established, we were able to examine Her symptoms of food sticking in the esophagus, pain and occasionally regurgitation began in 1943 An x ray taken early in 1944 is shown in Fig

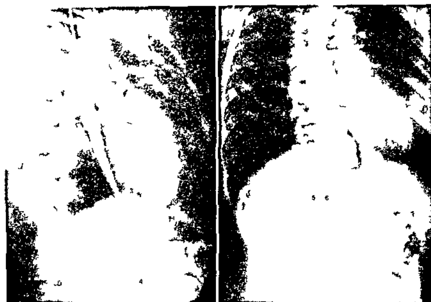


Fig 125 Appearance of barium filled esophagus shortly after onset of symptoms of cardiospasm and three years later Note initial hypercontractility with narrowing and ultimate diffuse dilatation

125 One can see a narrowed apparently hypermotile esophagus This finding was interpreted by the roentgenologist as evidence of esophagitis Three years later with symptoms persisting she had a dilated esophagus which was very hypermotile throughout the lower two thirds The existence of definite clinical cardiospasm was finally established at operation when an esophagogastrostomy was done

Figure 126 illustrates a similar sequence of events in reverse This woman in 1942 had a widely dilated hypermotile esophagus Her symptoms were those of sticking of food in the chest and regurgitation Her chief conflicts concerned her relationship with her mother and sister for whom she had become a sort of handmaiden It was possible to inculcate in her a somewhat

might bring about such a change was made on 11 healthy medical students Two noxae were selected, the ordinary painful experience of the 'cold pressor' test and a painful constriction of the head by a metal crown illustrated in Fig 123 Among these 11 subjects this latter experience with the head screw was associated with the symptoms and findings illustrated in *Table 16* Approximately one-third of the 11 subjects displayed cardiospasm similar to that induced in the girl previously mentioned who swallowed the cold and hot barium

Table 16 Symptom and Signs Observed during Experimental Stress (Headscrew) in Eleven Subjects

Weakness	8	Cardiospasm	4
Giddiness	6	Nausea	7
Diastolic hypertension	7	Vomiting	1
Bradycardia	1	Sighing	7
Sweating	10	Yawning	3
Flushing of skin	8	Latent tetany	3
Seborrhea	6	Photophobia	4
Pallor cold skin	5	Lacrimation	2

To these physical traumata was added in each case a symbolic threat in the form of an oral examination in Neurology Figure 124 summarizes the experi-

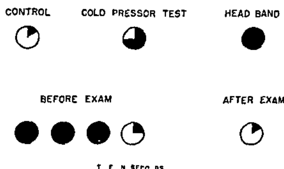


Fig 124 Delayed emptying in the esophagus in a normal subject induced by noxious stimuli from (a) cold (b) head pain and (c) conflict associated with school examination

ence in one of these subjects The small circles represent minutes, and the blackened portion of the circle the portion of the minute required for the barium to flow from mouth to stomach

During the cold pressor experience swallowing time was lengthened from ten seconds to forty-five seconds and to one minute while the head was pain fully compressed by the metal crown An even greater delay in the passage of barium through the esophagus, however, was induced by a symbolic threat

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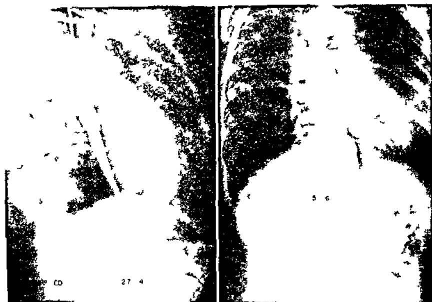


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more mature attitude toward her family and she was finally able to express her feelings toward her sister without feeling so much guilt. Concomitantly the widely dilated esophagus returned to a normal diameter and the swallowing time was so fast that with our slow spot film technic the barium could hardly be caught in the esophagus

Comment It would appear that the phenomena of esophageal hypermotility and cardiospasm occur as part of a biologic pattern of defense, which is appropriate when used against ingested irritants, but which is also used, less appropriately, by certain persons in their adaptation to more general stresses or threats to the security of the organism When this pattern is involved continuously or for long periods, as it is in certain "ruminative



Fig 126 A Typical picture of cardiospasm with extensive dilatation of esophagus and delayed emptying B, Decrease in diameter of esophagus associated with normal emptying time and absence of symptoms of cardiospasm ten years later following medical management with attention to life situation and personal conflicts

individuals, there is evidence that it may lead to the symptoms of dysphagia and ultimately to the structural deformities of cardiospasm

STOMACH

The next level of the gastrointestinal system, the stomach was investigated by way of our fistulous subject Tom He is shown in Fig 127 reclining on the laboratory table Midway between the umbilicus and xiphoid is his gastrostomy through which has herniated a generous collar of gastric mucous membrane It is possible for him to increase his intra abdominal pressure and force out any given amount of gastric mucosa for the examiner to inspect Usually we let him rest comfortably on the bed and simply keep the exposed area under constant observation, while gastric juice is collected by continuous siphonage and records of gastric motor activity are made from an indwelling balloon attached to a kymograph

Figure 128 summarizes the range of changes observed in this subject whom we have now studied approximately seven years The color of the gastric mucosa changed markedly from day to day from a pale yellow red to a deep

cardinal color When it was relatively red, the membrane was also engorged, thickened and the folds were fewer in number Measurements of blood flow through the organ by a special technic devised by Dr Charles H Richards



Fig 127 The subject Tom showing gastric fistula midway between umbilicus and xiphoid Through it protrudes a collar of exposed gastric mucous membrane

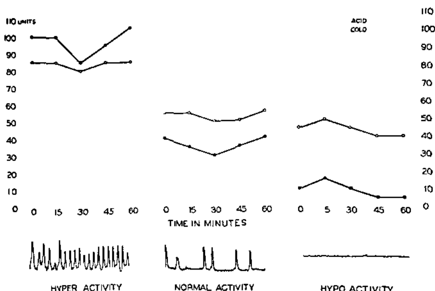


Fig 128 Correlation of measurable indicators of gastric function Note that hyperemia is associated with hypermotility and increased production of acid while pallor is associated with an absence of vigorous waves of contraction and low acid production

showed that redness reflected increased blood flow Associated with redness and increased blood flow hyperacidity and frequently hypermotility were observed Under average circumstances motor activity was intermittent and acid

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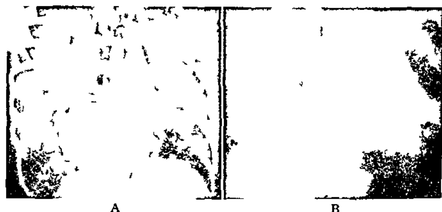


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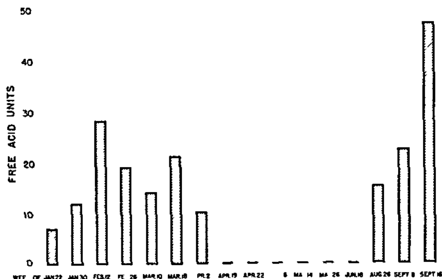


Fig 129 Protracted gastric anacidity during a period when Tom was overwhelmed and dejected.

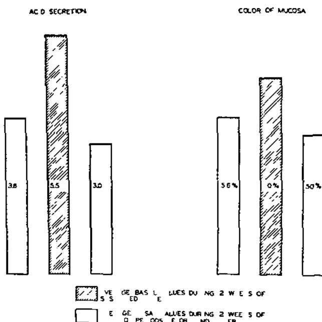


Fig 130 Sustained hyperfunction of the stomach during a period of conflict with resentment and frustration

demeanor was very different from that described above His movements were quick his voice was strong His stomach during this period was hyperemic and hyperfunctioning Finally, it was possible to obtain an increase in pay

and color were lower, and under circumstances of pallor of the mucous membrane, little or no acid was elaborated and there was no vigorous motor activity Under circumstances of sustained anxiety with resentment not only was the mucous membrane red but swollen The radial folds were fewer in number and the escaping gastric juice made even the skin of the abdominal wall red and raw looking Photographs taken by means of a speculum intro duced into the stomach through the stoma show the same variation

Hyperfunction was associated with fragility of the mucous membrane When the membrane in its average state was gently struck with a glass rod, no effect was noted, but such a slight trauma to an hyperemic, engorged membrane readily produced a small hemorrhage or erosion These all healed very quickly Furthermore, sustained engorgement was associated with a lowering of pain threshold When the average pale membrane was stimulated with a faradic current strong enough to burn the tongue, no pain was experi enced When the procedure was carried out on an engorged hyperemic mem brane, localized pain resulted Thus it is clear that the pain threshold is lowered during engorgement and even vigorous gastric contractions, ordinar ily not painful, become so during sustained engorgement

The alterations in gastric function which we observed, as in the case of salivary function, occurred in either direction Under certain circumstances Tom displayed marked gastric hyperfunction with the characteristic red, en gorged appearance, and under different circumstances of stress marked gastric hypofunction with pallor of the membrane

HYPOFUNCTION AND HYPERFUNCTION OF THE STOMACH

Figure 129 illustrates a situation of gastric hypofunction at a time when Tom was overwhelmed The incident concerned a technician of whom Tom was wary because she was in love He felt that she gazed out the window instead of at the burets and pipets On one occasion during an experiment in which duodenal fluid was being aspirated, she withdrew a small fleshy object through the tube, it was probably a little piece of clotted blood, but to Tom it was 'my own meat and part of the most important part of his anatomy He was intensely alarmed and frightened He walked about the laboratory for weeks thereafter, pale, listless and inactive He had no appetite, lost weight and day after day his ga tric juice failed to show any free acid The weeks from January to April with variable amounts of acid ranging up to 30 units are shown for comparison From April 19, the day following this episode, to April 26, the day after the technician was promoted to another type of job which wasn't in our laboratory, Tom s stomach was in an hypofunctioning state His general reaction was one of being overwhelmed

Figure 130 illustrates the opposite side of the coin, an episode which occurred at a time when Tom was being partly subsidized by a certain bene factor who meddled in his personal affairs The benefactor was attempting to dictate a family decision In considerable conflict, Tom finally defied the benefactor This time he reacted with anger and tension and his general

have shown that as the face may blanch or blush in varying situations of stress, so may the stomach become either hypoactive or hyperactive, depending on the situation and the individual

PEPTIC ULCER

Subjects with peptic ulcer for example, characteristically react to stress in the opposite fashion, i e, with gastric hyperfunction An example of such a reaction is provided by a forty seven year old Jewish lawyer who had had peptic ulcer for twenty years He was the only child of Russian immigrant parents His father was a quiet, reflective, religious man but the mother was intensely ambitious and hard working She and the father made severe financial sacrifices to provide the patient with an education He did well in college and law school, and during the course of these years he changed his name to a more easily pronounced, anglicized form He also married a Roman Catholic girl His parents disapproved of, but condoned this marriage Their principal concern was with their son s success in his career Shortly after graduation from law school, he was taken into a firm of all gentile lawyers He soon became heavily relied upon, and was doing much of the difficult work of the office The partners persistently failed however, to admit him to the firm This was the source of great disappointment and frustration, not only to himself but to his mother and wife, who, like his mother, was intensely ambitious It was in this setting that ulcer symptoms first developed

Finally, when it appeared that the partners could no longer exclude him from the firm they hired a second Jewish lawyer The head of the firm then told the patient that he felt it would not be justified to take one of these men and not the other into the firm This occasion was followed by a severe episode of gastrointestinal bleeding for which the patient was hospitalized Finally, at the outbreak of World War II, the younger Jewish lawyer was taken into the Army The older members of the firm were frequently preoccupied with matters outside the office and thus the patient s duties and responsibilities were redoubled He was virtually running the law office Despite the heavy work and long hours, his ulcer symptoms disappeared, and throughout the period of the war he felt well At the conclusion of the war, however his associate returned from the service unharmed and again the frustrating situation was resumed The patient s epigastric pain recurred and became incapacitating leading finally to readmission to the hospital After a few days of rest, encouragement and strong reassurance and while taking alkalis and frequent feedings his symptoms again subsided

At this point he was intubated with a balloon attached to a kymograph (Fig 132, *A*) Gastric motor activity of an average type was recorded until suddenly an interview was conducted in which the patient was asked why he had failed to meet his mother s ambitions and whether or not he felt that her sacrifices in his behalf had been justified Almost immediately gastric contractile activity became enhanced He showed no evidence of tension or nervousness at first He gave a restrained well-organized and forceful justification of his life As the account proceeded, however his voice became

for Tom from the hospital and thereby he was able to throw off his benefactor The gastric hyperfunction concomitantly subsided

Figure 131 is illustrative of an individual who characteristically reacted to stress with gastric hypofunction and the usual associated symptoms of epigastric fullness, anorexia and nausea She had been rejected by both parents, had reacted to life problems with indecision and had attempted to resolve them by rationalization rather than by action She felt that her own security and that of the Jews in general depended heavily upon the success of the Zionist movement She was intubated with a gastric balloon connected to the kymograph During a phase of relative comfort and relaxation with gastric contractions of average frequency and amplitude, her attention was called to a newly formed society dedicated to opposing the Zionist movement and exposing what they considered misrepresentations by the Zionists She had not

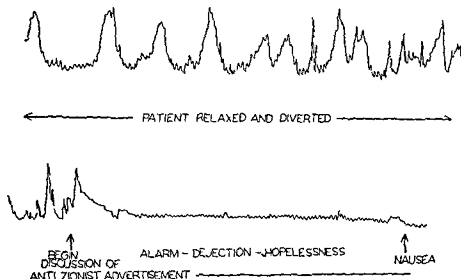


Fig 131 Interruption of gastric motor activity induced by a discussion of relevant personal conflicts

previously heard of the society, and she appeared horrified to learn of their activities Pale and wide-eyed she stared at the examiner, immobile and obviously frightened The motor activity in her stomach promptly stopped The organ relaxed and increased in size Finally, nausea occurred The gastric changes are illustrated graphically in Fig 131 Later discussion revealed that this individual characteristically reacted to threatening situations with anxiety in which there were strong feelings of hopelessness and despair "When something comes up to worry me, I have a feeling of being defeated, that things are hopeless That is how I felt when you showed me that advertisement of the anti-Zionist organization"

This type of gastric disturbance seen commonly among soldiers in the horrifying anxious circumstances of combat was recognized several years ago by Walter Cannon, and it was long thought to be the only way in which the stomach reacted during stress In recent years, however, numerous workers

have shown that as the face may blanch or blush in varying situations of stress, so may the stomach become either hypoactive or hyperactive, depending on the situation and the individual

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stronger, and he became restless, red faced and tense, and the gastric contractions were associated with localized epigastric pain The interview was allowed to continue for ninety-four minutes, when he was given 0 3 gm of sodium amytal intravenously (Fig 132, *B*) At this point, gastric contractions stopped abruptly His pain was promptly relieved, and his entire manner was

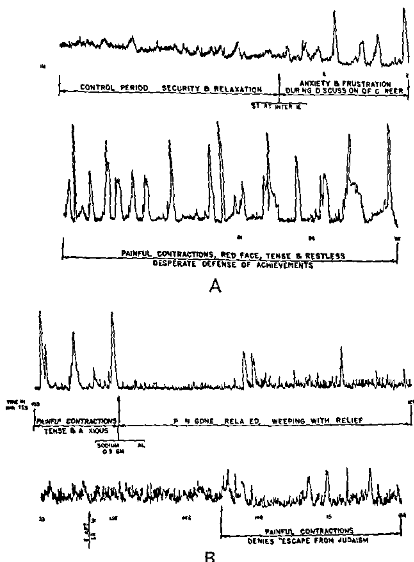


Fig 132 Hypermotility of the stomach associated with epigastric pain in a subject with peptic ulcer during discussion of relevant personal conflicts

altered He clung weeping and sobbing to the examiner s hand, saying ' I ve tried so hard, so hard " He said that he finally felt relaxed, and was weeping with relief After twenty minutes of freedom from pain, and while still under the influence of sodium amytal, a second interview was begun in which it was suggested that his change of name, his marriage to a Roman Catholic and his

association with a gentile firm might represent an attempt to escape from identification with Judaism Again his manner became restrained, his flow of conversation even and forceful Gastric contractions were resumed, and although they were of much smaller magnitude, they were nevertheless painful

A second example of this phenomenon supported by direct visual observation is that of a sixty seven year old Merchant Marine tugboat chief engineer who developed obstructive symptoms with persistent vomiting and emaciation three weeks prior to his admission to the hospital He had noted weakness and vague epigastric discomfort, but he had had no history of pain suggestive of peptic ulcer except for a brief episode thirty years before which lasted only a few weeks X-ray examination, however, demonstrated an ulcer with gross distortion of the duodenal cap The stomach was dilated and emptying greatly delayed Free acid in the gastric juice was 15 and total 38 Stools were negative for occult blood, but red cells in the peripheral blood numbered only 3 to 4 million with 11 5 gm hemoglobin An exploratory operation confirmed the presence of the obstructive ulcer in the region of the duodenal cap A posterior gastroenterostomy was performed to relieve the obstruction and postoperatively a Miller Abbott tube was left in place The latter apparently damaged the esophagus in some way because a progressive narrowing with final occlusion of the esophagus occurred over a period of three weeks Because of the esophageal stricture a gastrostomy was done The stoma measured approximately 5 cm in diameter and through it herniated parts of a few engorged gastric rugae It was accordingly possible to study this subject in the same manner in which experimental c were made on Tom

The experiment was carried out thirteen hours after the last with the subject reclining comfortably on a couch The gastric mucosa continuously observed under standard lighting conditions Gastric juice siphoned through a Levin tube and motor activity was recorded on a kymograph from an inlying inflated balloon During approximately forty five minutes of control period the subject was lightly diverted and continuously reassured As already noted, the membrane during this period was already moderately engorged (3+) and hyperemic (60 on the color scale) Gastric juice was elaborated at the rate of approximately 20 cc every fifteen minutes, it was moderately viscous and opaque with free acid remaining in the neighborhood of 15 units Abruptly he was asked whether his own and his wife s ambitions had been satisfied by his becoming a tugboat engineer His manner became serious and slightly grim but he maintained that the work had been entirely satisfactory He was then asked where a tugboat engineer stood in the social constellation of men who had qualified as chief engineers His even manner continued although tension was evident by this time and he wiped a tear from each eye He was further asked about possible conflicts with his wife He denied conflicts, but the denial was associated with additional lacrimation and within one half hour of the start of this interview the gastric rugae had become intensely red (80) and engorged, completely filling

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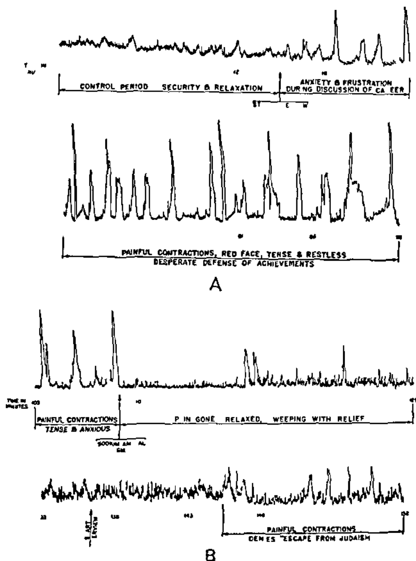


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association with a gentile firm might represent an attempt to escape from identification with Judaism Again his manner became restrained, his flow of conversation even and forceful Gastric contractions were resumed, and although they were of much smaller magnitude, they were nevertheless painful

A second example of this phenomenon supported by direct visual observation is that of a sixty seven year old Merchant Marine tugboat chief engineer who developed obstructive symptoms with persistent vomiting and emaciation three weeks prior to his admission to the hospital He had noted weakness and vague epigastric discomfort but he had had no history of pain suggestive of peptic ulcer except for a brief episode thirty years before which lasted only a few weeks X-ray examination however, demonstrated an ulcer with gross distortion of the duodenal cap The stomach was dilated and emptying greatly delayed Free acid in the gastric juice was 15 and total 38 Stools were negative for occult blood but red cells in the peripheral blood numbered only 3 to 4 million with 11 5 gm hemoglobin An exploratory operation confirmed the presence of the obstructive ulcer in the region of the duodenal cap A posterior gastroenterostomy was performed to relieve the obstruction and postoperatively a Miller-Abbott tube was left in place The latter apparently damaged the esophagus in some way because a progressive narrowing with final occlusion of the esophagus occurred over a period of three weeks Because of the esophageal stricture a gastrostomy was done The stoma measured approximately 5 cm in diameter and through it herniated parts of a few engorged gastric rugae It was accordingly possible to study this subject in the same manner in which experimental observations were made on Tom

The experiment was carried out thirteen hours after the last feeding and with the subject reclining comfortably on a couch The gastric mucosa was continuously observed under standard lighting conditions Gastric juice was siphoned through a Levin tube and motor activity was recorded on a kymograph from an inlying inflated balloon During approximately forty five minutes of control period the subject was lightly diverted and continuously reassured As already noted the membrane during this period was already moderately engorged (3+) and hyperemic (60 on the color scale) Gastric juice was elaborated at the rate of approximately 20 cc every fifteen minutes, it was moderately viscous and opaque with free acid remaining in the neighborhood of 15 units Abruptly he was asked whether his own and his wife s ambitions had been satisfied by his becoming a tugboat engineer His manner became serious and slightly grim, but he maintained that the work had been entirely satisfactory He was then asked where a tugboat engineer stood in the social constellation of men who had qualified as chief engineers His even manner continued although tension was evident by this time and he wiped a tear from each eye He was further asked about possible conflicts with his wife He denied conflicts, but the denial was associated with additional lacrimation and within one half hour of the start of this interview the gastric rugae had become intensely red (80) and engorged, completely filling

the area of the stoma Motor activity became intense and sustained and free acid rose to 35 units No pain was noted

Comment The cause and mechanism of peptic ulcer are still unexplained, but a large body of experimental evidence supports the view that this disorder, in many instances at least, occurs as a sequel to disturbed gastric function in reaction to significant stresses in the life situation The steps which support this formulation are briefly as follows

1 The stomach in peptic ulcer is hyperfunctioning as regards engorgement, blood flow, acid production, motor activity and emptying time

2 Gastric hyperfunction accompanied by epigastric pain of typical "ulcer" type may be induced in human subjects by exposure to situations involving significant personal conflict

3 Such gastric hyperfunction is apparently mediated through the vagus innervation, and is associated with two serious physiologic hazards (a) a lowering of the pain threshold in the stomach and (b) increased fragility of the membrane

4 Gastric juice kept in close contact with a minor erosion leads to further gastric hyperfunction and may result in the establishment of an ulcer

5 In subjects with peptic ulcer gastric hyperfunction may be accentuated with the production of hyperacidity, hypermotility and pain by a vigorous discussion of significant personal problems

COLON

The colon too has been found to participate in the human organism s reaction to stressful life situations An unusual opportunity to study these relationships was afforded in the persons of 2 human subjects with areas of colonic mucous membrane exposed on the abdominal wall The one illustrated in

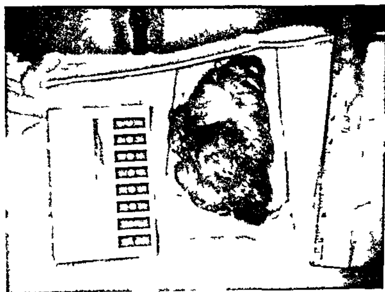


Fig 133 Evaginated exposed area of sigmoid colon in a fifty year old human subject

Fig 133 was a fifty year old man who had a sigmoidostomy thirteen years before because of a rectal stricture presumably from lymphogranuloma inguinale His colonic mucous membrane was of fairly normal appearance although it had herniated through the sigmoidostomy and a loop of bowel nearly a foot long lay evaginated on the abdominal wall In Fig 133 is shown the appearance under average circumstances The blood vessels are readily visible in a relatively pale smooth membrane which is hanging loosely from its attachment During the course of a conversation in which he gathered the impression that we felt that this rectal stricture had come to him as a result of homosexual activity he became intense and resentful, red in the face, hot

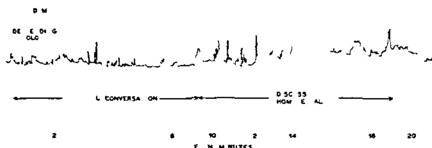


Fig 134 Hypermotility of the sigmoid colon of subject illustrated in Fig 133 during discussion of relevant personal conflicts

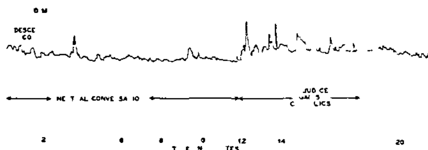


Fig 135 Hypermotility of the sigmoid colon of subject illustrated in Fig 133 during discussion of relevant personal conflicts

under the collar and the segment of bowel became narrowed with corrugated surface reddened and hypermotile

Figure 134 illustrates the tracing from a balloon in the sigmoid colon obtained while this experiment was in progress

Figure 135 illustrates the same sort of response on another day during a discussion of prejudice against Catholics

LYSOZYME CONCENTRATION

Karl Meyer has observed that individuals who have ulcerative colitis have a very much higher lysozyme concentration in the stool than do healthy subjects Moreover he has been able to produce lesions in the gastrointestinal

tract of dogs by feeding lysozyme Accordingly, we measured lysozyme in several of our subjects from day to day to determine whether or not this enzyme system varied in association with life situations and emotional states Some of the variations are shown in Table 17 Normal values of lysozyme

Table 17 Variations in Concentration of Lysozyme in Stools of Human Subjects with a Variety of Conditions

Condition	Units per gram of wet stool
Normal subjects	0 3– 1 7 units per gram of wet stool
Acute congestive heart failure	1 2
Cancer of the large intestine	3 2
Mucous colitis, (mild cases)	
(a) Constipation	0 6
(b) Diarrhea	0 4– 1 5
Ulcerative colitis	
Remission	0 7– 1 6
Mild symptoms	13 0– 25 0
Moderate severe symptoms	40 0–100 0
Regional enteritis, remission	0 4– 0 8
Acute (twenty four hour) gastroenteritis	0 7

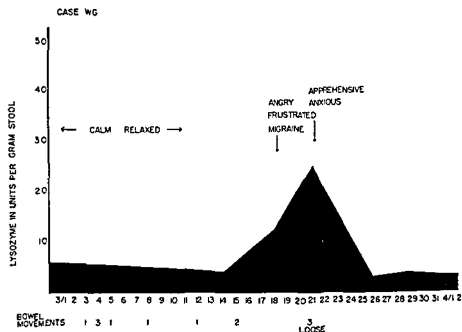


Fig 136 Minor increase in lysozyme concentration in a stool of a normal subject during emotional conflict

were found to be usually below 1 2 Figure 136 shows a minor rise in lysozyme concentration during a period of apprehension associated with an attack of migraine

Figure 137 shows the variations in lysozyme concentration in a young man, who had one episode of ulcerative colitis three years ago but was healthy at

the time of the observations His lysozyme during periods of relative security was normal below one unit, but when he was going to take to his home his fiancee, whom his parents had not met and whom he was sure they would not

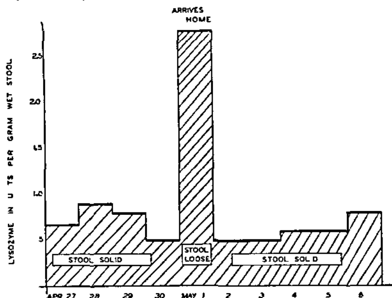


Fig 137 Transitory increase in lysozyme concentration in a stool of a subject who had ulcerative colitis during a period of serious personal conflict.

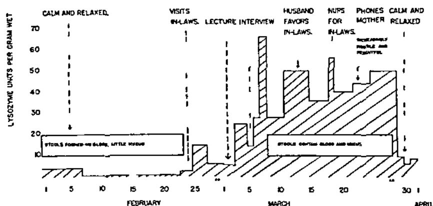


Fig 138 Correlation of life situation and attitude with the concentration of lysozyme in the stools of a patient with ulcerative colitis Note that bloody stools occur during the periods of greatest concentration of lysozyme

approve of, he had a bout of diarrhea associated with increase in lysozyme concentration to 2.5

Figure 138 shows the variations in a woman with ulcerative colitis It illustrates how lysozme increase antedates the appearance of blood in the stool

In Fig 139 is shown the second subject whose exposed bowel was studied In this instance, it was the right colon, that is, the cecum and the ascending colon and a small bit of ileum, which lay evaginated on the abdominal wall This lesion resulted from a sequence of operations performed for ulcerative colitis They culminated in an ileostomy so that the exposed part of the bowel was not connected to the fecal stream Under average circumstances the colon was relatively pale and relaxed as shown in Fig 139, but upon discussing his sister-in-law about whom he had special conflicts and resentments, there occurred the same change noted in the other fistulous individual The bowel became contracted, hyperemic, corrugated and much more active Finally, when this same sister in law, while this patient was still in the hospital, moved

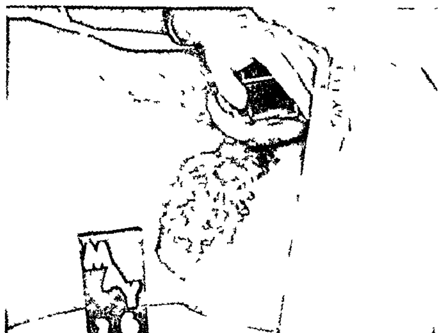


Fig 139 Evaginated exposed area of cecum and ascending colon of a twenty six year old human subject with ulcerative colitis

into his house and took over his own quarters, he suffered an acute exacerbation of his ulcerative colitis The exposed stoma shrank to a quarter of its former size and tiny ulcerations appeared around the edges and in the center of the lesion He began passing blood and mucus from his rectum and his ileostomy discharge became cloudy and foul Following the subsidence of this event his colon resumed its former appearance and the rectal and ileal discharges disappeared

Figure 140 shows the variations in lysozyme in this individual correlated from day to day with his life situation and emotional state Lysozyme values as high as 100 were noted during periods of conflict with resentment and low lysozyme values below 20 occurred when this individual was relatively calm and secure

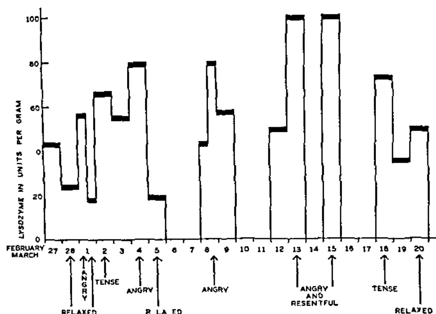


Fig 140 Correlation of life situation and attitude with the concentration of lysozyme in the surface mucus removed from the subject illustrated in Fig 139

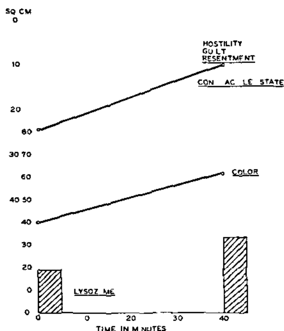


Fig 141 Hyperemia of the colon associated with increased contractile state and increased production of lysozyme in the subject illustrated in Fig 139 during a discussion of relevant personal conflicts

Figure 141 illustrates a short term experiment in which lysozyme was raised from 20 to 30 units and at the same time the contractile state and color were increased in association with discussion of a significant personal conflict

Another such experiment is shown in Fig 142 The subject initially came to the laboratory intensely angry and resentful because the nurses had allowed him to oversleep He was a highly fastidious person who always kept his dressing neat, cleaned his fingernails and combed his hair He was humiliated and angry to have to appear before us in a disheveled condition with a dirty dressing Lysozyme concentration was very high, but following a period of reassurance and diversion with relaxation, lysozyme concentration decreased

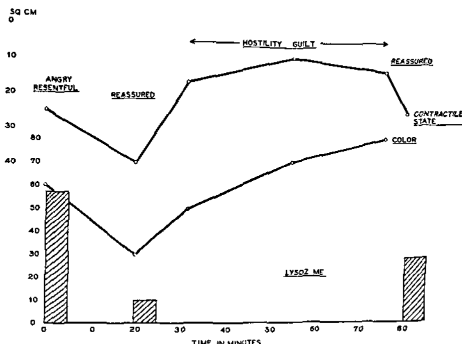


Fig 142 Decreased redness associated with relaxation of the colon and diminished production of lysozyme in the subject illustrated in Fig 139 during a period of reassurance followed by hyperemia increased contractile state and increased lysozyme production during a discussion of relevant personal conflicts

Later, while discussing with him his relationship to his mother, which provoked hostility and guilt, the colon became hyperactive again associated with an increased elaboration of lysozyme It was also possible to provoke this type of reaction by discussing this man s relationship to his other mother, the Veterans Administration, and to observe the same type of changes associated with an increase in the lysozyme concentration

Comment In the colon not only was hyperfunction recognized in response to stressful life situations which induced a reaction of resentment and suppressed hostility, but, as in the case of the stomach, hypofunction too was evident when the subject was dejected and depressed

CONCLUSION

Thus it appears from these data that most of the levels of the gastrointestinal tract are likely to participate in the human organism s reaction patterns to threatening events in the life situation, including those threats which arise out of problems of interpersonal adjustment It further appears that changes of hyperfunctioning with associated muscular overactivity, hyperemia and changes in local secretions, at first altogether functional and transitory, may, when unduly sustained, lead to structural damage and disease

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THE ROLE OF THE INTERNIST IN THE CARE OF THE NON-PSYCHOTIC PATIENT WITH FUNCTIONAL GASTROINTESTINAL COMPLAINTS

EDWARD WEISS, M D

DR BOCKUS *Our next discussion will be by one of Philadelphia s, if not America s, pioneer psychosomaticists He probably won t like that introduction, but he usually has a very good comeback*

DR WEISS There is no such thing as a psychosomaticist Psychosomatic medicine is not a specialty, it is a point of view and an approach which applies equally to all medical and surgical problems It must not become a specialty But I submit that as a concept it has a very great deal to do with your specialty, and we have only to look at these beautiful slides and hear this excellent discussion of Dr Wolf s to see how tension of emotional origin can disturb physiologic mechanisms I think there can be no clearer demonstration that here is a problem that must concern you every day in the practice of gastro enterology

It is not surprising that gastrointestinal physiology can be disturbed by the emotions, by feelings, because during the first few years of life the feeding state and the feeling state become indissolubly related so that, depending upon the love and security that go with the feeding process or the anxiety and insecurity that go with it, definite patterns of behavior are laid down which can be called forth later when certain life situations reawaken old associations Thus it is that every kind of a personality from normal to psychotic may use the abdomen as the sounding board of the emotions Therefore the functional disturbances of the gastrointestinal tract become one of the most important problems with which you deal, and yet you know from your formal undergraduate medical education, and your postgraduate efforts since, the scant attention which is paid to this major part of your practice If we would only gauge our educational efforts in that manner we would realize the disparity

between what we teach and what we practice It s not difficult to cite statistical studies to prove these assertions

INCIDENCE OF FUNCTIONAL GASTROINTESTINAL DISORDERS

A study by Friess and Nelson[1] of New York on 269 consecutive psychoneurotic patients in an out patient department showed that 41 per cent presented gastrointestinal symptoms as their major complaints As you know there is also abundant evidence from military experience of the importance of functional disorders of the gastrointestinal tract—how preeminently this system stands out to mirror the disturbances in our emotional life Brill made a study of 600 consecutive psychoneurotic cases encountered in Army General Hospitals and found that 29 per cent presented gastrointestinal disturbances as their major difficulty 14 per cent were in the cardiovascular field and 9 per cent in the musculoskeletal system I could continue with such evidence regarding functional disturbances of the gastrointestinal tract

We may also consider the organic problems as you well know, peptic ulcer became a major problem in World War II and there has been considerable discussion as to why neurocirculatory asthenia, so called was such an important problem in World War I, while gastrointestinal disorders especially peptic ulcer became such an important problem in World War II

I have some information furnished by Dr W C Menninger,[3] who was head of the Consultant s Divi ion in Neuropsychiatry in the Surgeon General s Office during World War II The incidence of peptic ulcer in World War I was 0 71 per thousand In World War II it rose to 2 75 certainly a significant increase There are probably a number of reasons but I will not go into that problem because Dr Bockus wants me to discuss the question of how the internist deals with functional problems of the gastrointestinal tract So I speak to you as an internist, and not as a psychiatrist and that s a very different problem because you all know that when a patient comes to the psychiatrist he comes prepared to discuss himself as a person, but when he comes to a general physician he comes prepared to discuss himself as a medical case, looking for a physical cause for his trouble And now, what do you do about that? How do you handle these various problems that present themselves in such abundance in your every day practice?

PSYCHOSOMATIC DIAGNOSIS

I know that some of you rarely admit the possibility of functional disturbances of emotional origin In other words, there are certain physicians, reared in the organic tradition in medicine who study their patients by vari ous tests and instruments of precision and are never willing to admit that there isn t a physical cause for the trouble if they are just thorough enough, and the studies are just continued long enough They can always find another reason—metabolic endocrine allergic obscure infection—to continue their investigations until the patient ends up as a chronic invalid, often with an abdomen criss-crossed by the marks of surgical exploration Because the

surgeon too is drawn into this exploration of the abdomen for a pain which really exists in the spirit of the patient

I'm very familiar with specialists who only admit the presence of the psyche when the patient becomes psychotic Fortunately this is not as true today as it was a quarter of a century ago One of the great reasons is that military medicine did something for the psyche, it made it respectable Physicians who served in the military forces and who returned to civilian practice came back with a healthy respect for the psyche as a force in making people sick, they had learned to pay just as much attention to emotions as they did to germs and bullets In fact I think it might well be said that psychiatry was established on a firm scientific basis in World War I, and World War II has seen its more complete integration into general medicine When that integration is completed I think there will be little need for the term "psychosomatic," because good medicine will be psychosomatic Then we will approach every patient, especially in gastroenterology, with three questions (1) What *kind* of a person are we dealing with, no matter what his disturbance? What are his physiologic and psychologic characteristics, inborn and acquired? (2) What has he *met*, not what has he 'et, which is the question most often asked, and upon which almost every patient tries to blame his illness What has this predisposed person met in his environment—what noxious influence, whether it be germ, allergen, or mother in law? And (3) What *happens* as a result of the meeting of this predisposed individual and this noxious influence in his environment?

When we ask ourselves these questions we no longer make the faulty distinction between organic and functional We regard a sick human being as a biologic organism that can be disturbed by a variety of factors, and illness may therefore be the result of a number of causal factors acting in complementary fashion Therefore psychosomatic diagnosis consists not simply of an effort to exclude or evaluate organic disease by the traditional organic methods, but in addition consists of personality studies In other words, it is a complementary technic, a supplementary technic, and not an exclusive technic To put it another way, these patients with functional disturbances of their gastrointestinal tract have distinctive features in their personality that can be discovered by a study of the emotional life What does that mean in plain words? It means that we have to satisfy certain postulates in regard to psychosomatic diagnosis just as we do in regard to organic diagnosis We have first of all to know whether the individual has a family background of psychopathology, we have to know whether his early history indicated emotional disturbance—in other words, childhood neurosis, we have to know whether his personality structure is the kind that can be touched by certain specific emotional events, and then we have to cross section his life history and see whether there is a relationship between the onset of the illness and an emotionally disturbing event that is specific for his personality Not all people respond in the same way

I well recall a middle-aged woman who came to me several years ago suffering from an ailment that I found obscure I could not make a diagnosis

At first I thought it was some cardiovascular problem, she was a rather negative neutral looking dejected individual, and I applied all of the organic tests that I knew and could discover no cause for her illness Soon she drifted away but returned a number of months later looking transformed She had a vigorous step, a healthy look different clothes, rouge and lipstick, a new hat, in short, she was an entirely different person and completely well I learned that her husband had died! He had been an alcoholic and she had been ashamed of it, she had never discussed it with anybody and had suffered in silence the hurts and humiliations that frequently go with living with an alcoholic When he died she had relief instead of grief I simply cite this as an exaggerated illustration of the fact that the emotional event must be specific for the personality It is not enough simply to inquire of a patient, Are you worried about anything? We have to know more about psychodynamics than that

Finally in our diagnostic study we must be prepared to discuss these problems with the patient Just as an allergic patient may be hyposensitized to a particular allergen, so some of our neurotic patients can be hyposensitized to a particular psychic trauma, or if not, again in the analogy to an allergic disturbance, we can perhaps change the environment to remove the individual from the sensitizing substance If we satisfy these criteria, we have established, together with our clinical study a psychosomatic diagnosis And now what do we do about it? Should we slap the patient on the back and say, Forget it it s all in your head, as we sometimes do Should we send the patient on a vacation (and the farther the better!) even though he takes his troubles with him, or should we make an effort to understand the patient as a human being—to look for the person in the patient That I submit is a job which rightfully belongs to us and we ve got to know something about it The day is past when the gastroenterologist can perfect himself in the various physiologic technics of gastroenterology to the exclusion of psychologic technics, and still consider himself well trained

PSYCHOSOMATIC ASPECTS OF TREATMENT

How then do we go about handling our patients with functional disturbances? How far should we go what is our job? It seems to me that there is a minor and a major psychotherapy just as there is a minor and a major surgery, and that minor psychotherapy must be understood by the man who practices general medicine, and gastroenterology particularly He s got to be able to understand the various emotional problems that can disturb the workings of the gastrointestinal tract Let me cite an example

Dr Wolf s interesting presentation of cardiospasm recalled to me one of the first patients that brought my attention to psychosomatic medicine, although it wasn t called that then Many years ago at Jefferson I met a patient on Dr Chevalier Jackson s service who had cardiospasm with a markedly dilated esophagus He was a poor English druggist, who gave the usual medical history of his condition He said that his illness had begun about eight or ten years before and had been progressive He had consulted many physicians

Discouraged, he had invested a large sum of money with an osteopath who had promised cure, finally, very sick and without funds, he had come to the hospital The previous medical history did not seem to bear upon this illness

His life situation, however, was interesting He had been born into the drug business" and had never known anything except the long hours and tedious work of an underpaid pharmacy clerk He married young and five children came in rapid succession It was a great financial struggle to look after them About 1916 or 1917 while working very hard he had ' some kind of a breakdown ' during which there were nervous symptoms and he took bromides In 1922 his oldest and favorite son, then aged twenty, had just obtained an excellent job which paid well He gave his salary to his mother and the father was overjoyed with the finally achieved prospects of economic freedom He had always pictured a great career for this able son and had looked forward to his financial aid to help him in his old age

Without warning one morning shortly afterward he learned that this son had just secretly married He said, "It was the greatest blow I ever received, not only because of the financial part of it but the way he did it' (that is, secretly) The patient went on to say, "I felt like a child crying until his heart would break and he placed his hand on his epigastrium to show where he felt the blow

He could not get over this disappointment and even considered having the marriage annulled on the basis that the boy was too young to marry It was interesting to note, however, that he himself had married at the same age He harbored a great deal of resentment toward the girl s parents who, he felt, had stolen his fine son from him It was during this period that attacks of swallowing difficulty occurred and grew more pronounced and more frequent

A short time later further aggravation occurred He learned that his brother in England, whom he described as a ne er-do-well, was cheating his mother of her small legacy He went to England, brought his mother back and she then made her home with them It seemed significant that the mother con tributed her sole income to the upkeep of him and his family In other words, while he accused his brother of having "bled his mother" he himself had already borrowed money from her and then took her weekly allowance for living expenses His altruism in rescuing her from his ne'er do well brother seemed questionable

The picture was that of a meek, submissive and dependent individual who had always worked hard without achieving success, strongly identified with his oldest son in whom he hoped to achieve the success denied himself With his son's secret marriage came a tremendous disappointment from which he could not recover

An interesting commentary in line with our thesis was his experience with the osteopath He consulted him around December 1931, and was charged $1000, which his sons had to borrow, for the management of his case' It was interesting to consider why he felt like investing this great sum of money with the osteopath He said, ' The osteopath told me that my trouble was due

to a spasm arising from a shock, and the patient went on to say, He did not know about my son's marriage He was much impressed by this diagnosis 'because it was the first time that any doctor had suggested that shock and worry might be responsible for my trouble He therefore placed his entire confidence and all the money he could raise in the osteopath s hands

In the recital of his story, accompanied by great emotion this poor druggist made the following significant and perhaps revealing statement, "My son s marriage was a bitter pill that I could not swallow And who can say that that was not, at least, one meaning of the illness?

Now, what I m suggesting is that certain disorders of the gastrointestinal tract have symbolic significance I m not trying to say that all cases of cardiospasm represent life situations which the individual cannot swallow, but what I do say is that you may study cardiospasms as you will, dilate them as you please, use such medicines as you think are indicated, but unless you study the personality and life situation of the patient with cardiospasm you have not made a complete study and you are not in a position to treat that patient from a comprehensive standpoint I think that unless there is an x-factor in the constitutional make up of that individual he can encounter all kinds of situations in life which stick in his craw' and he won t get cardiospasm but give him the predisposition and a specific emotional problem and you have a combination which spells cardiospasm, and the same reasoning can be applied to various other disorders of the gastrointestinal tract

Finally I would like to outline some of the *principles* of management of patients with functional disturbances, of the gastrointestinal tract or elsewhere One, I would suggest that we give the patient time to tell his story, and I know that you will say this is next to impossible in the kind of busy practice that many of you conduct But it can t be helped There are certain patients, especially those with chronic disorders who cannot be understood unless they are given time to tell their story If you are too busy during office hours to listen to them then you must set aside some time and give them a special appointment when you can take the time to listen Or send them elsewhere Unfortunately for the cause of psychosomatic medicine there are many physicians who have tremendous practices and who never think about the psyche in other words patients who have functional disturbances can get temporary relief from symptoms by physical means alone largely through the doctor-patient relationship I know a man who accumulated a very large practice giving injections, the injections were made up of vaccines gathered from the various mucous surfaces of the body from mouth to anus Many of his patients did exceptionally well for a time and he misguided fellow, thought that he had the answer He had a dynamic personality and he didn t realize that with each injection he was giving a little bit of his personality to strengthen some of these immature people If we want to understand these patients—if that is our goal, rather than the accumulation of a large practice—then we ve got to understand something about the emotional life, and we ve got to be willing to listen, rather than talk I know that s very hard to

do, it is hard to teach ourselves this very important discipline of listening to patients rather than talking to patients, but it pays off in dividends of understanding what makes them sick

In other words, I would suggest that we get to know the patient as a person rather than just as a medical case We have to look for the person in the patient

Next, I would suggest that our physical examination be complete and such laboratory studies as are necessary be done because there's no reason why a neurotic cannot develop a cancer or other organic disease, any more reason than that he can't get hit by a truck But I would also suggest that when we have excluded or evaluated physical disease, we put a stop to physical study and think in terms of behavior

Then I think it is very important to reassure patients concerning the absence of cancer, what with our present-day cancer propaganda all those who enter your office, especially women, have cancer in the back of their minds They don't always express it, it comes out at the end of the interview, in the last thirty seconds as they have their hand on the door and are about to leave You have said, 'I can find no evidence of organic disease,' and they smile and say, 'Well, I m so happy, Doctor, because I was a little afraid I was developing a cancer " They don t say that in the beginning of the interview, then it s a lump, or a bump, or a swelling, or a pain, or its some peculiar symptom which hides the cancer thought

It is important to explain to patients, 'Your trouble is a disorder and not a disease "It isn't colitis—it's irritable colon, and then it's not difficult to tie it up with emotional disturbances You've got to explain that the trouble is real, it s not imaginary, but it s caused by the tension of inadequately expressed feelings They must not be led to believe that you think their trouble is imaginary, because it s not, and they rightfully resent that implication If disease is present, and there is a functional overlay, it must be explained that symptoms are out of proportion to disease—disability is more pronounced than the disease would account for Finally, it is important to explain the time relationship between the onset of the illness and the emotionally disturbing event

It's important to encourage discussion of personal problems, especially within the family setting It's the group who sit down at the table at night who focus the irritations and tensions which cause bodily disorders Whether or not anything can be done about the situation it helps the patient to discuss the problem with an objective listener

I always ask the patient to tell me what *he* thinks of the illness It s extraordinary the explanations that you get from patients as to what they think is the cause of their trouble, and it's the first hurdle that you have to get over in an effort to help them As long as they have some fanciful idea as to the cause of the illness and don t tell you about it you can't do anything with them Get it out on the surface and reeducate them along physiologic lines

I think it is important to urge patients to do *more* instead of *less* We always slap patients on the back and say go home and take it easy, and we play right

into their hands to stay sick I encourage them to do more, ' to carry on in spite of symptoms, and when they do you can watch their 'cancer pains evaporate

If drugs are used I think we ought to explain what they are and what they do We sometimes give medicines with a mystery still surrounding them from the days of old Patients are intelligent enough to understand what they re taking and why, and what we expect from them

Lastly, we must try to desensitize patients by talking about emotionally disturbing life situations, and if desensitization is unsuccessful we sometimes can manipulate the environment in an effort to help them

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DR BOCKUS *I have never previously heard a talk which had such an important message for the gastroenterologist as that of Dr Weiss I wish that these messages from Doctors Weiss and Wolf could be broadcast throughout the length of this land*

PERSONALITY STUDY OF PATIENTS WITH ORGANIC DIGESTIVE TRACT DISEASE

HERBERT S GASKILL, M D

DR GASKILL I think I know how the proverbial fifth wheel feels, after hearing the two presentations that have just been given It seems almost superfluous to ask a psychiatrist to participate on this program when the psychiatric implications have been so well demonstrated

I m not going to try to discuss the entire field of personality studies in gastroenterological diseases, I will limit myself to peptic ulcer and trust that this will give you an idea of some of the psychiatric thinking in gastroenterologic problems

Dr Weiss pointed out that when the infant is born, very early a connection is established between receiving food and being loved I think the perceptive mother always must have been aware of this on the other hand this has been amply confirmed by such studies as those of Ribbel We all know how a child uses his stomach to express feeling Thus when an infant is angry it may vomit rejecting the food it has eaten again in an older child one may see changes in appetite, anywhere from just the pickiness of not wanting certain kinds of food to the refusal of all food and vomiting as in anorexia nervosa Then again one may see functional constipation—the refusal to do what

do, it is hard to teach ourselves this very important discipline of listening to patients rather than talking to patients, but it pays off in dividends of understanding what makes them sick

In other words, I would suggest that we get to know the patient as a person rather than just as a medical case We have to look for the person in the patient

Next, I would suggest that our physical examination be complete and such laboratory studies as are necessary be done because there's no reason why a neurotic cannot develop a cancer or other organic disease, any more reason than that he can t get hit by a truck But I would also suggest that when we have excluded or evaluated physical disease, we put a stop to physical study and think in terms of behavior

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the parents expect because they have put too much pressure on the child in one area or another and he or she feels rejected

PSYCHOPATHOLOGY OF PEPTIC ULCER

The recognition of psychologic factors in peptic ulcer is not a new concept Physicians have always commented on the emotional disposition of their ulcer patients, but frequently in very vague terms such as "neurogenous" or "neurogenic" Studies such as those of Draper have emphasized the body build and constitution of these patients as important factors in predisposition, but most authors have described a predictable type of personality Typically the ulcer patient was the aggressive, go-getter business man who was loaded with responsibilities and who had little or no opportunity for relaxation

Precise psychologic studies of the psychopathology of ulcer patients did not appear until relatively recently Alexander and his associates, after studying psychoanalytically a group of ulcer patients, concluded that the typical conflict situation was of more fundamental importance than a specific personality profile, and I believe that this concept has never been seriously challenged The conflict for these patients is their strong passive-dependent receptive wishes which they attempt to repress Although finding the same type of central conflict in their patients Romano et al described three distinct personality types

Each individual in the process of growing up seeks to be productive and independent The adult, with persistent infantile desires in the direction of *passivity and dependence, for example the wish to be loved and cared for,* attempts to repress these strivings as completely as possible During infancy these wishes normally find satisfaction in association with feeding as we have mentioned And so to be fed becomes unconsciously equated with the idea of being loved If this feeling relationship between mother and child is interfered with either quantitatively or qualitatively, the passive receptive-dependent wishes are intensified, persisting as signs of immaturity in the adult personality When these receptive needs continue beyond their normal expectancy, the individual is more demanding but these excessive demands cannot be realized in every-day living This leads to further emotional maladjustment by creating hostility The conflict over the dependent needs in childhood may be masked by its relative normalcy at that *developmental* stage, but as the individual matures, the adult giving loving role is expected particularly in our society which puts such emphasis on independence and competitiveness The receptive wishes, therefore, are largely denied All such denial produces irritation, anger and hostility, the degree of hostility being proportional to the amount of frustration This hostility may be expressed directly, or through personality defense mechanisms Part of the aggressiveness seen in ulcer patients unquestionably is derived from this This hostility and the resulting character deviations often complicate therapy and must be adequately resolved to effect a cure I do not need to mention any of the physiologic studies demonstrating the role which the emotions have in alter

ing gastric function because they've been so amply brought out already by Dr Wolf

THE PSYCHIATRIC STUDY OF ULCER PATIENTS

Psychiatric study of peptic ulcer patients who were routinely seen in the Gastro-intestinal Clinic at the University Hospital is the basis of this report The study was undertaken partially to evaluate the personality profiles of these patients and partly to widen the therapeutic base for these patients by including short term psychotherapy as an adjunct to their medical and surgical treatment Sixty-eight peptic ulcer patients were evaluated, 46 men and 22 women They ranged in age from thirteen to fifty-four years The intensity of the psychiatric study varied widely A few patients were seen only once while occasional patients were seen in excess of 50 to 75 visits The psychotherapeutic interviews were generally an hour in length The vast majority were seen from 5 to 10 times All of these patients had the usual configuration of partially repressed passive dependent wishes To this was added however, hostility, which was a prominent symptom The various defense mechanisms by which these patients attempted to resolve this psychopathology resulted in four general categories of patients or personality types No specificity is claimed for these types No doubt another psychiatrist using the same material might have summarized them quite differently A brief description of each of these groups is as follows

Group I The aggressive, ambitious individual who generally holds a position of responsibility successfully They are superficially gregarious individuals whose outward independence is paid for with a constant pattern of tension and anxiety of which the patient is well aware Their energetic behavior which accounts for their outward success is an overcompensation for their repressed dependent wishes Their hostility is clearly evident in their poor interpersonal relationships in many instances They are generally extremely competitive and egotistical resulting in envy and jealousy Consequently they create considerable friction in their relations with other people which eventuates in further deprivation of their receptive wishes This is the group which has most commonly been described as the ulcer personality

Group II This group consists of energetic, moderately successful persons who show rigid restricted personality traits They are shy and submissive, rarely allowing any outward expression of their hostility They are indecisive overly conscientious and stubborn They flourish on routine and order They are less gregarious than the first group Their interests are few but more intense Their dependent needs frequently find partial resolution in a close dependent relationship with another person who symbolically represents a parent This may be an actual parent, a marital partner or a person outside the family Any disturbance in this dependent relationship immediately intensifies their anxiety and hostility and threatens their adjustment They have marked conflict concerning this dependency Under their submissiveness there is much hostility and resentment but it is rarely expressed because of their guilt

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Group III This group is composed of extremely shy, sensitive individuals who have little capacity to fulfill their needs or wishes Their hostility is pre dominantly directed toward themselves, as evidenced by their extreme submissiveness and dependence Their dependence is obviously manifest, they frequently appear to be living an almost parasitic existence Their achieve ment in any area of human conduct is low Each rebuff, no matter how unin tentional or slight, which the environment administers to their feeble con structive endeavors is followed by retreat to a more passive and dependent existence This regression borders in some on a schizophrenic reaction as in an occasional patient when fantasy largely replaces constructive behaviour

Group IV These patients have marked character disturbances as evidenced by their impulsiveness and inability to learn through experience Due to their failure to sustain a responsible level of conduct, they are generally ineffectual in earning a living Alcoholism and homosexuality frequently complicate the picture Many are rebellious and hostile with paranoid trends, they are openly demanding but are constantly frustrated in their dependence

I want to give two cases that illustrate two of these personality types

The first is a forty-five year old male, of Irish extraction, who was the youngest of four children He was seen in the Clinic over a period of almost four months, generally twice a week The parents were strict but moderately affectionate, and devout Catholics He had a grammar school education As a child he was conscientious and set high standards of achievement for himself He was picky about his food and had frequent bouts of indigestion He started work as a trolley conductor, but rapidly became a supervisor He was married at the age of twenty-one to his first wife She was unfaithful Six years later they were separated, she died one year later He married subse quently and this marriage was very happy During this period his vocational *responsibilities increased greatly and coincidentally he developed* consider able tension manifested by anxiety, bouts of depression, indecision, fatigue and insomnia and recurring peptic ulcers At twenty four he had his first attack of epigastric pain and indigestion on days when his work was par ticularly trying At this time he became aware of his wife s infidelity A few weeks later his first duodenal ulcer was diagnosed by x-ray The ulcer healed under medical treatment and shortly after that he was separated from his wife, and he was asymptomatic for some years

The abnormal conditions prevailing during the war years made his job more trying and he had a return of his symptoms which eventuated in a succession of ulcers, four in all during a period of three years

When he was *first evaluated psychiatrically it was decided that this patient* might be able to benefit from an interpretive short term psychotherapy and that possibly even on this basis some therapeutic change might be effected In the early visits he was tense and restless but attempted to repress all feel ings, particularly his hostility He had marked feelings of inferiority and was dependent and demanding Gradually he became aware of these attitudes, and the conflict they produced He also became increasingly aware of his hostility and resentment which resulted from the demands made on him due

to the responsibilities entailed by his job As these problems gradually were worked through, he noticed a diminishing amount of tension His ulcer also had completely healed

When last seen, he related the following incident A few days before a passenger standing on a station platform threw himself in front of the elevated train in which the patient was riding He experienced momentary epigastric pain and resentment over the task ahead of him but he quickly tackled his responsibilities in a mature manner which he completed with no further evidence of tension or anxiety He ended by stating "I now feel well I am secure and relaxed and feel perfectly confident to do the job which is required of me

The second patient was a forty-eight year old colored man who had had ten ulcers prior to his present duodenal ulcer He had been born in the South and finished the fifth grade of grammar school, leaving to go to work to help support the family, he always had been very dependent on his mother The other children thought that he was her favorite and that he was spoiled As a child he recalled quite clearly that he had occasional bouts of ' G I symptoms, Very much like what I have now He had been picky about his food. When he was twelve years old his mother had to be hospitalized for a psychosis and did not return to the home She had always been nervous

In 1916 he married a year later joined the Army and was overseas during World War I On returning he found his wife was indifferent to him and furthermore she was pregnant by another man He was not openly vindictive about her infidelity since he had done some running around and she was entitled as he put it, to the same consideration However, as her indifference and rejection of him became more marked his bouts of gastrointestinal distress increased in frequency, resulting in his first diagnosed ulcer in 1928

From then on he had ulcers repeatedly, sometimes for two or three years he would not have an ulcer, but as his wife became less willing to meet his dependent needs the recurrence of the ulcers came closer together Eventually she asked him to leave He did, although he continued to support her and the six children, including the one which was not his He then started to live with another woman At this point he was first seen by the psychiatrist The projected therapeutic goal in this case was to improve his adjustment within the present situation

His conscience troubled him since he was very religious, being a deacon in the church He had guilt, bouts of depression and much resentment towards his wife Later he came to accept this relationship as being the only alternative open to him It apparently went along well because it met his needs When I come home at night she has my food ready, just the things I like to eat the kind of things that mother used to prepare for me In every way she was solicitous of his needs

Eventually his ulcer healed he was relaxed denied any depression and discharged himself from the Clinic He was not seen again in the Clinic for almost six months and then one day he came in complaining of exactly the same symptoms The gastroenterologist who saw him referred him immedi

ately to our Clinic after confirming the diagnosis of ulcer by x-ray His story was as follows

About three weeks earlier the woman with whom he had been living decided to get a job at the shore and leave for the summer, and as he said, 'You see, she really didn't care very much for me, she didn't love me if she could go and leave me at a time like this I was so dependent on her, I needed her so badly ' After she left he had become very depressed and discouraged and his ulcer symptoms had returned

Within a relatively short period of time, psychotherapy, combined with medical care, had relieved the tension and depression and the ulcer was healed

These two cases have been chosen to demonstrate certain aspects of this study The first patient was classified as belonging in group II Using short term dynamic psychotherapy the patient was made aware of his dependent receptive needs Considerable reintegration was effected so that he was able to meet his responsibilities more maturely and without crippling tension A specific instance demonstrating this improvement was cited The patient considered this an extreme test and felt that it indicated his growth and ability The second patient was classified in group III The goals in therapy were limited to largely supportive treatment The reactivation of the ulcer when the specific emotional vulnerability was touched is amply demonstrated The dynamic equilibrium in the patient had not been changed so that life incidents which threatened his passive dependent needs produced the same emotional maladjustment with physiologic alterations ending in ulcer

In conclusion, emphasis should be placed on the central conflict—i e , the more or less repressed passive dependent-receptive needs—as the etiologic agent for the gastric dysfunction The personality is the end result of the entire psychobiologic history of the individual Consequently, the personality is the total of all these experiences, reflecting much more than just one developmental stage The result is the diversified personality types discussed

FUNCTIONAL GASTROINTESTINAL DISTURBANCES IN PSYCHOTIC REACTIONS

JOSEPH C YASKIN, M D

The functional gastrointestinal disturbances in psychotic reactions are not nearly as important as in the psychoneuroses, with some notable exceptions Nevertheless, the internist, and especially the gastroenterologist, should have a clear concise formulation in his mind regarding the role of psychoses in his specialty

In the interest of clarity, it is best to define what is meant by psychosis and

psychotic reactions There is no satisfactory medical definition for psychosis The best definitions are as much legal as medical The following definition was found useful in practice—an insane person is one in whom there exists, due to disease, a more or less prolonged deviation from his normal method of behavior and who is, therefore incapable of managing his own affairs or transacting ordinary business, who is dangerous to himself, to others, or to property, or who interferes with the peace of society

The psychoses should be differentiated from the so-called psychoneuroses, which is not always easy to do

Also for practical purposes, it is important to bear in mind that there are three psychotic types of reaction, namely, the organic, affective and schizophrenic

1 The organic reaction type, such as occurs in structural diseases of the brain due to vascular and degenerative changes, neoplasms, infections intoxications and deficiency states, and characterized by psychotic predominantly intellectual, difficulties

2 The affective reaction type comprising principally the cyclic manic-depressive reactions and involutional melancholia

3 The schizophrenic reaction type, with many bizarre modes of thinking, feeling and acting observed in various types of dementia praecox

THE EVALUATION OF GASTROINTESTINAL COMPLAINTS

Bitter Taste in the Mouth This symptom is an almost constant complaint in patients with depressions, even in those having the so-called extramural depressions which are often misdiagnosed with the subject being treated for colitis (Yaskin[1])

Anorexia is a constant and prominent symptom in almost all patients with depressions Some depressed patients complain that they feel hungry but cannot eat that everything tastes alike or is tasteless Many depressed patients have no appetite in the morning, but can tolerate or even enjoy a meal in the latter part of the day With the onset of recovery the appetite for meals in the earlier part of the day improves The writer has frequently observed that in patients with malignancy masked by depression the appetite is at its best in the early part of the day and decreases as the day goes on Failure to eat is frequently observed in schizophrenics in whom it may be due to apathy, lack of interest, catatonic negativism or delusional states Anorexia is a common symptom in persons having organic psychotic reactions

Bulimia, polyphagia and acoria as well as excessive appetite may be observed in some patients who are feeble minded as well as in those with paresis senile dementia and schizophrenia The latter may also evince a tendency to swallow things other than food (pica), even their own excrement (coprophagia) Pica or depravities in appetite are rare in the psychoneurotic individuals

Anorexia alternating with ingestion of excessive quantities of food is often observed in persons with early and borderline schizophrenia sometimes accompanied by diet ceremonials These phenomena usually represent morbid

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tion of many of the psychoses, but especially of the depressions Fecal impac tions are frequently found in psychotic patients The depressed patient s bowels may fail to move because of atony or psychomotor retardation or delusional states In the schizophrenic, retention of the feces is observed in catatonic negativism, in delusional states, but most commonly it is due to apathy and inattention

Vomiting is rarely seen in the schizophrenic but is not uncommon in the tube fed depressed patient who makes every effort to terminate his life

Hypochondriacal and nihilistic delusions, such as those in which the patient is convinced that his bowels are obstructed and that the stomach is cancerous, are most common in patients with involutional melancholia, but may be seen in those in the early stages of dementia praecox The psychopathology of these delusions is interesting

In reviewing the various gastrointestinal disturbances encountered in psychotics, one readily observes that the same manifestations may occur in con junction with the several types of reactions It seems that the psychotic dis turbances are reflected in changes of secretion (Dunbar[4]), motility, and sen sation at the vegetative-visceral level, but, in addition, misinterpretations and elaborations at the psychic level occur, resulting in hallucinatory and delu sional formations The early recognition of the underlying etiologic psychotic process is of more than academic importance With recent advances in the treatment of psychotic patients, especially those with manic-depressive and involutional melancholia, in whom gastrointestinal complaints are early and/or prominent symptoms a timely diagnosis means not only shortening the time of suffering and prevention of suicide but effective immediate treatment In schizophrenia the advances in treatment are less spectacular, but there are those who believe that early insulin shock therapy plus psychotherapy results in some recoveries and, in many, arrest of the progress of the disease

EMOTIONAL DEPRESSION

Emotional depression is an important subject from the standpoint of internal medicine, and especially gastroenterology, and deserves special consideration The evaluation of the emotional state should be a routine part of every clinical examination

The early detection of emotional depression is of special value Emotional depression occurs (1) as a normal fluctuation in otherwise well integrated persons or as a reaction to appropriate precipitating causes (reactive depression), (2) in the course of the severe psychoneurotic states and (3) in associa tion with many of the psychoses as in schizophrenia, secondary to structural and chemical abnormalities, and more particularly, in manic-depressive reac tions and in involutional melancholia

DIAGNOSIS

The first requisite for the diagnosis of depression is the *consciousness of the existence* of such a clinical entity and the fact that it is frequently masked by

impulses (actions carried out without reflection and aimful willing), but may be due to delusional trends

PAIN PARESTHESIAS AND DYSESTHESIAS

These phenomena referred to the abdomen and perianal region are common in persons with constitutional psychoses and require careful evaluation They may occur as early and monosymptomatic manifestations in dementia praecox patients and especially in those with involutional melancholia Indeed, in persons having the latter disease they may receive considerable attention from the organically-minded internist who fails to observe the associated personality disturbances In some instances many useless investigations and operations are performed before the patient shows the fundamental evidences of agitated depression and anxiety

Abdominal pain, usually combined with constipation, often masks depressions of the manic-depressive type The well developed case of emotional depression with its unmistakable attributes of difficulty in concentration and application (retardation) or agitation, insomnia, anorexia and eventually self blame with suicidal tendencies is indeed easily recognized However, in many patients the symptoms begin and continue to be predominantly somatic, the symptoms being referred to any organ in the body, most commonly the abdominal viscera These patients are often treated only for the somatic complaints until spontaneous recovery occurs in several months or they progress to a frankly psychotic state with occasional suicidal attempts Of course, depressions may be associated with structural diseases so that a careful diagnostic survey must include exclusion of organic disease The diagnosis of the basic depression, which is so frequently masked by somatic complaints, is aided by the presence of the following (1) a family history of manic-depressive psychosis which occurs in about 40 per cent of the cases, (2) previous episodes of mild depression or hypomania with complete recovery after several months, (3) previous attacks of somatic complaints similar to the present attack with complete recovery after several months, (4) the disturbance of the sleep cycle, (5) the loss and perversion of appetite with loss of weight, (6) bitter taste in the mouth, (7) interference with the outflow of energy clearly out of proportion to the somatic complaints, (8) feeling of unreality, (9) the observation that all the symptoms are worse in the morning or after sleep, and (10) the absence of primary somatic structural or chemical disease

MOTOR DISTURBANCES OF THE ALIMENTARY TRACT

Cardiospasm is common in association with the psychoneuroses, but is rare with the psychoses, although vague difficulties in swallowing are fairly common early manifestations of involutional melancholia (Faulkner et al [2]) Less commonly, achalasia of the cardia is observed in subjects having depressions of the manic-depressive type when the cyclic emotional disturbances are masked by the predominant complaint of difficulty in swallowing

According to Henry,[3] gastrointestinal motor dysfunction may be present in association with most of the psychoses *Constipation* is a common manifesta-

tion of many of the psychoses, but especially of the depressions Fecal impactions are frequently found in psychotic patients The depressed patient s bowels may fail to move because of atony or psychomotor retardation or delusional states In the schizophrenic, retention of the feces is observed in catatonic negativism, in delusional states, but most commonly it is due to apathy and inattention

Vomiting is rarely seen in the schizophrenic but is not uncommon in the tube fed depressed patient who makes every effort to terminate his life

Hypochondriacal and nihilistic delusions, such as those in which the patient is convinced that his bowels are obstructed and that the stomach is cancerous are most common in patients with involutional melancholia, but may be seen in those in the early stages of dementia praecox The psychopathology of these delusions is interesting

In reviewing the various gastrointestinal disturbances encountered in psychotics one readily observes that the same manifestations may occur in con junction with the several types of reactions It seems that the psychotic disturbances are reflected in changes of secretion (Dunbar[4]), motility, and sen sation at the vegetative-visceral level, but, in addition, misinterpretations and elaborations at the psychic level occur, resulting in hallucinatory and delusional formations The early recognition of the underlying etiologic psychotic process is of more than academic importance With recent advances in the treatment of psychotic patients, especially those with manic depressive and involutional melancholia, in whom gastrointestinal complaints are early and/or prominent symptoms a timely diagnosis means not only shortening the time of suffering and prevention of suicide but effective immediate treatment In schizophrenia the advances in treatment are less spectacular, but there are those who believe that early insulin shock therapy plus psychotherapy results in some recoveries and, in many, arrest of the progress of the disease

EMOTIONAL DEPRESSION

Emotional depression is an important subject from the standpoint of internal medicine and especially gastroenterology, and deserves special consideration The evaluation of the emotional state should be a routine part of every clinical examination

The early detection of emotional depression is of special value Emotional depression occurs (1) as a normal fluctuation in otherwise well integrated persons or as a reaction to appropriate precipitating causes (reactive depression) (2) in the course of the severe psychoneurotic states and (3) in association with many of the psychoses as in schizophrenia, secondary to structural and chemical abnormalities, and more particularly in manic-depressive reactions and in involutional melancholia

DIAGNOSIS

The first requisite for the diagnosis of depression is the *consciousness of the existence* of such a clinical entity and the fact that it is frequently masked by

somatic complaints It is important to remember that organic and/or metabolic disorders may be the primary cause of emotional depression However, the coexistence of physical disease and emotional depression may occur in the absence of cause and effect relationship It is of importance for therapeutic purposes to differentiate the depression of the manic-depressive type and involutional melancholia from that due to other psychiatric conditions, especially the psychoneuroses The avenues to a correct diagnosis in these cases are threefold (1) an evaluation of the personality make-up in terms of the patient's dynamic response to educational, economic, social and marital adjustments, at least some knowledge of the efficiency of performances prior to the onset of the present illness, and a record of the occurrence of previous "nervous breakdowns or masked episodic illnesses, (2) complete physical examination and reasonably necessary laboratory procedures, followed by judicious interpretation of objective findings, especially with the view of avoiding fads and insignificant abnormal findings, and (3) a repeated and careful evaluation of the mental status with special attention to the emotional state, to preoccupation with physical complaints and to the various criteria previously discussed under the heading of abdominal pain

Somatic diseases may cause emotional depression in formerly well integrated persons This is particularly true of organic abdominal diseases (Yaskin[5], Weisenburg, Yaskin and Pleasants[6]), but many other debilitating organic diseases may produce depression The occurrence of organic disease in persons who have a predisposition to depressive reactions presents difficulties in diagnosis and treatment This has been discussed elsewhere Here it may be emphasized that the association of organic disease with mental disturbances *requires the utmost caution, acumen and judgment on the part of the clinician* He must be expert enough to evaluate the roles played by the underlying personality pattern, the organic factors and the associated emotional disturbances in order to arrange a therapeutic regimen taking into account all of these factors

The evaluation of depression in the schizophrenic is often difficult, requiring prolonged observation and considerable psychiatric experience

The differential diagnosis of depression in manic depression and involutional melancholia from the psychoneurotic disturbances is of practical value and is not always easy The majority of the psychoneuroses have their inception early in life These patients by their symptoms and obvious maladjustments usually reveal the inadequacy of their personalities ' The neurotic personality is one in whom the neurotic symptoms are built into the character (Jones[7]) Neurotic episodes are readily precipitated by a variety of causes and the symptoms have a marked variability The episodes are irregular and there is rarely complete freedom of symptoms between attacks In the majority of patients the outstanding symptom is not depression but anxiety and its various substitutes (Yaskin[8]) *A better contact with 'reality is noted in the* psychoneurotic patients They are more amenable to suggestion and other methods of psychotherapy than are depressed patients It should be stressed, however, that profound depressions with genuine suicidal tendencies at times

complicate the psychoneuroses, especially the compulsive-obsessive states and less frequently the anxiety hysterias

TREATMENT

The following suggestions for treatment of patients with depression in association with gastrointestinal disturbances are offered First, all avoidable surgical operations should be discouraged Likewise unnecessary restrictions in diet and special treatments directed for relief of functional organic complaints should not be undertaken These procedures only increase the patient s preoccupation with his somatic complaints and his depression

For patients with severe depression in the absence of physical contraindications such as heart disease hypertension tuberculosis and severe diabetes electrocerebral shock therapy is indicated

If the depression is of lesser severity or if electrocerebral shock therapy is contraindicated, the treatment is largely symptomatic Many patients are benefited by hospital care chiefly because it relieves them of many annoying responsibilities and permits the utilization of a properly supervised regimen including occupational therapy Psychotherapy has its place but it is important to remember that unlike psychoneurotics the depressed patients are not usually responsive to suggestion and shoulder slapping They are genuine sufferers and he who wishes to encourage must have a deep appreciation of their tortures Sedation at bedtime is often necessary General hygienic measures including tonics and the arrangement of a proper colon stasis regimen are indicated Lastly, it should not be forgotten that even the mildly depressed patient is a good candidate for suicide and necessary precautions should be taken

In summary then, functional gastrointestinal disturbances are not prominent features in the course of major psychotic reactions There is one notable exception and that is the occurrence of depressions which require early and accurate evaluation from the standpoint of treatment

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COMMENTS FROM THE PHYSIOLOGIST

SEYMOUR S KETY, M D

DR BOCKUS *I thought it might be refreshing to have a man come from the physiologic laboratory and in his role of the pure physiologist comment on these psychosomatic relationships about which we have been hearing*

DR KETY Dr Gaskill was worried about the fact that he felt like a fifth wheel at this conference, and from what Dr Bockus has said, I suppose my function is that of the windshield wiper We have heard a very interesting analogy made by Dr Weiss, in a thoroughly charming manner, of the comparison or the contrast between the psychoanalytic theory of the origin of disease and the bacterial theory of the origin of disease I have a suspicion, from speaking to psychoanalysts, that there is a feeling of resentment or envy among this group (if such people can have such feelings) toward the bacteriologists, who have a theory which is established, which everybody accepts and which never is made a subject for debate

Strangely enough, the bacteriologist also resents the psychiatrist A professor of bacteriology once told me that he was very envious of the psycho analysts because these men have developed a beautiful theory and then go out and make money with it without ever bothering to prove it I told him that was not a very fair comment upon psychoanalysts I said there are some psychoanalysts who are endeavoring to prove their theory, and also many physiologists who are trying to substantiate their theories for them I think that we will all agree that Dr Wolf's presentation represents a remarkable example of the way in which the psychoanalytic approach to organic disease or to disease in general can be subjected to scientific critique and objective demonstration

You see the psychoanalyst has quite a problem on his hands On the one hand, we have the mind—with its hostilities, its resentments, its loves for

daughters and dislikes for sons, all of these intangible, immaterial sort of phenomena—and on the other hand, and separated by quite a distance, we have—the gut. The problem which the psychoanalyst has to solve is how a thought of hostility—a thought which cannot be measured, which cannot be weighed, which has no dynes of force behind it—can produce, let us say, an erosion or an ulcer of the gastric mucosa. That is the problem: that gap between the mind and the body—a tremendous gap which must be bridged. There are some people who think that those two aspects are worlds apart, and that they can never even approach each other.

With a more hopeful attitude, I think that something can be done to make these spheres approach each other. I think that Dr. Wolf has tried it from the direction of the gastrointestinal tract onward. I think that Dr. Gaskill has given us an example of how the approach can be made from an objective examination of the mind.

My function for the next few minutes will simply be to point out the work of others, neurophysiologists, who have tried to bridge that gap between the mind and gastrointestinal disease. Since we don't know much about the mind, or at least I don't know much about the mind, suppose we start, not with the mind, but with the gut and work up a bridge in the general direction of the mind. I am not so naive as to believe that we will ever really bridge that gap, at least we can approach more and more closely to an actual junction.

THE AUTONOMIC NERVOUS SYSTEM

Starting then with the gastrointestinal system and going toward the mind the first mediating mechanism that presents itself is the autonomic nervous system. I need not tell this group the physiologic effects of the autonomic nervous system on the gastrointestinal tract, I'm sure you know them far better than I. In addition, however, to the fact that the sympathetics relax the gut and increase the tone of the sphincters, another significant function is their ability to constrict the blood vessels of the gut. This is important from the point of view of the economy of the rest of the body and also possibly important as a mechanism whereby disease can be produced in this mental-organic complex. It is well known that in hypotension the sympathetic nervous system goes into a prolonged discharge, and in severe shock it has commonly been found that there are gastrointestinal erosions or hemorrhages into the gut which can hardly be explained except on the basis of profound, prolonged vasoconstriction which results in anoxia. There are certain reflexes which can be said to exist between the sympathetic nervous system, or at least the autonomic nervous system, and the gut and other nerve pathways. One such reflex is illustrated by the fact that serious trauma of any kind may cause a burst of sympathetic activity to the gastrointestinal tract along with other regions. It is a well known clinical observation that trauma, especially to the head, may be followed after a period of three days by the vomiting of food which was ingested just before the accident occurred. Here we have an example of prolonged gastric retention, probably or possibly on the basis of such a reflex mechanism.

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but a large amount of information has been gathered from the operation of frontal lobotomy in which the frontal lobes may be dissociated from the rest of the brain and possibly traumatized Watts and Fulton found that there was a high incidence of fatal intussusception in animals who were subjected to bilateral frontal lobotomy Others have reported pylorospasm and hyper motility of the stomach after frontal lobotomy, and a very common symptom after this procedure is a tremendous increase in appetite and a tendency toward obesity

Sweet and his coworkers report a massive gastrointestinal hemorrhage from the esophagus and stomach in a patient after a prefrontal lobotomy Strassman has reported 26 cases of acute hemorrhagic ulcerations and 28 cases of per forations of the esophagus and duodenum in patients with a variety of cerebral lesions not necessarily confined to the frontal lobe

So we see at least in this very cursory examination that there is some relationship between the brain and the gastrointestinal tract, and if we assume that there is a relationship between the mind and the brain, we have made at least one step in an attempt to associate gastrointestinal disease with mental disturbances or mental phenomena However we must realize that the mere fact that these pathways exist is not in itself evidence that they are in operation either normally or in the induction of pathologic states In this connection, I am reminded that Dr Batson has been able to inject the cerebral venous system completely by injections in cadavers of the dorsal vein of the penis We may gather from that accomplishment that there are direct communications between the venous systems of these two structures but we would not immediately jump to the conclusion that normally or even in disease there was any flow of blood from one vascular bed directly to the other In the same way the mere fact that these pathways exist in the central nervous system is not in itself evidence that they are normally functioning or that they operate to produce disease

However, I should like to say that the work of Dr Stewart Wolf and other research along similar lines will certainly help to put psychosomatic medicine on a sound, physiologic basis I venture to say that if enough scientists are permitted to wander into the no man s land between mind and body, the day may come when Koch s postulates, or criteria quite as objective, may be applicable to the psychosomatic etiology of human disease

PANEL DISCUSSION

Question Dr Wolf do you prefer to treat cardiospasm by psychotherapy as opposed to other methods of treatment?

Dr Wolf I feel as both Dr Weiss and Dr Gaskill do If there is evidence that situational conflicts are relevant to the development of this or that bodily disturbance therapy should involve consideration of the life situation and

THE HYPOTHALAMUS

Going farther up the tract from the autonomic nervous system, we come to the next site where the brain, at least, may influence the gastrointestinal tract in the hypothalamus. The hypothalamus represents the important integrator organ of the autonomic nervous system. It lies above the optic chiasm and the sella turcica and contains nuclei that apparently integrate both the sympathetic and the parasympathetic nervous system. It is said that the posterior and lateral nuclei regulate the sympathetic nervous system and the anterior medial integrate the parasympathetic system. At any rate, it can be demonstrated in the laboratory with experiments in monkeys that stimulation of the anterior and medial parts of the hypothalamus produces an increased gastric pressure, increased peristalsis of the gastrointestinal system, and that this is mediated through the vagus. If the vagus is cut these results are no longer obtained. Stimulation of the posterior and lateral aspects of the hypothalamus produces what appears to be sympathetic stimulation: a decrease in gastric pressure and a loss of gastric and intestinal motility.

There are also observations upon what happens to the gastrointestinal tract when the hypothalamus is destroyed or damaged. Symptoms of severe hyperphagia and obesity occur in some cases. Gastrointestinal hemorrhages have been found in patients and in animals in whom the hypothalamus has been injured. There have been ulcerations of the mucosa, of the esophagus, the stomach, the small intestine; these ulcerations and hemorrhages are partly mediated through the sympathetic nervous system, and in a sympathectomized animal damage to the hypothalamus no longer results in gastrointestinal hemorrhage, although there may be some other lesions of this tract. There have been cases of perforated duodenal ulcers occurring in animals and in man when the hypothalamus was injured. Cushing attributed the severe gastrointestinal disturbances which accompany many types of brain trauma and brain surgery to damage to the hypothalamus. Thus we see that at least a part of the brain can exert a great deal of influence on the gastrointestinal tract.

THE CEREBRAL CORTEX

But the hypothalamus is not as close as we can get to *the mind in our* examination. We can follow the hypothalamus up until we get to the cerebral cortex and that, I venture to say, is as close as we can get to this interesting phenomenon, the mind, at least in an approach from somewhere in the body.

There are direct cortico-hypothalamic pathways which go from the hypothalamus to various parts of the cortex, predominantly to the frontal lobe and especially to the orbital surface of the frontal lobe. It has been found that by stimulating these cortical areas evidences of increased or decreased gastrointestinal motility can be achieved, at one place or another, and again changes in sphincter tone or in intragastric pressure. Psychic gastric juice is well known to depend on an intact cortex.

What happens when the frontal lobes become damaged, either by trauma or by operation? There has been some animal investigation upon this point,

The cause of depressions is unknown It is my feeling that a true depression and I m not speaking of psychoneurotic depressions is just about as psychologic as diabetes mellitus or pernicious anemia, and therefore the cure of these patients will depend on specific agents, but we don t know these agents yet Perhaps Dr Wolf and Dr Kety will furnish us with the desired information, and I want to make it a matter of record that some of the young men here will live long enough to know that depressions of the manic-depressive type and involutional melancholia will be treated chemically just as diabetes and pernicious anemia are now

Question Would you continue to disregard loss of weight and the finding of fecal occult blood in a patient with irritable colon of definite psychosomatic origin all studies for gastrointestinal pathology being normal?

DR YASKIN I would not Occult blood to me is occult blood—whether it comes from an irritable colon due to a disagreement with a mother-in-law or whether it is due to a carcinoma that Dr Bockus and the X ray Department can t find I ve had a few of those in my time—that s no reflection on Dr Finkelstein and his group or Dr Bockus Occult blood is always occult blood and you have to look for its cause and I m not prepared yet to accept carcinoma as being of psychosomatic origin

Don t laugh at me, because a colonel, whose name I do not remember about eighteen months ago published a paper on peptic ulcer in the South Sea Islands and he said Take this island and they have no peptic ulcers, take this island it s full of peptic ulcer Why? On this island they re all happy and tranquil and get along well and therefore have no peptic ulcer, on that island they are war like, resentful hostile and they have peptic ulcer

Well, I wouldn t have any quarrel about that—he may be right but there may be other factors that he doesn t know about If he should tell me that on the same island there is no carcinoma because there is no hostility, and on the other island there is a lot of carcinoma because there is hostility, I fear I should develop cardiospasm because I cannot swallow this line of reasoning as yet

Regarding the loss of weight, this should always be evaluated carefully Loss of weight is common in the psychoneuroses and psychoses but it is all too true that these groups of patients may develop organic disease such as carcinoma accounting for the loss of weight As for the treatment of loss of weight in the psychoneuroses especially severe cases with insomnia anxiety tension, diarrhea and vomiting, it is best not to push psychotherapy for the first week or so As a matter of fact, the clinician sees to this as a matter of sheer necessity for psychotherapy at this stage is not possible After the acute stage is over sedation and other measures are gradually discontinued and psychotherapy proceeds as indications arise As you probably know, psychotherapy does not consist in the doctor telling the patient what to do He guides him to get well by leading him to reevaluate his attitude toward him self, toward his various physical and mental processes and toward the various

attitudes of the subject If other factors appear to be of special importance, they should be dealt with No therapy need be used to the exclusion of some other approach

Question The individual does not live in a vacuum If his psychopathology reflects the psychopathology in his social environment, should we not begin directing efforts in the direction of social psychiatry found in the cultural groups?

DR GASKILL I think one could answer that very readily by saying yes We must work with the social background as well as the psychopathology of the individual There is a very interesting article in the recent Bulletin of the Menninger Clinic which you might be interested in reading, an article on "Rural Psychiatry" In it the need for understanding the family group in order to treat the patient is stressed I think that often has not been sufficiently stressed in urban psychiatry, and that it is frequently of as much importance to treat intimate members of the family as the patient

Question Most general hospitals have groups of patients with functional gastrointestinal disorders especially at certain seasons of the year What do you think of the value of group psychotherapy as a part of the therapy program in such cases?

DR YASKIN I think there is no doubt that group psychotherapy is beneficial, but unfortunately in my experience many gastrointestinal disturbances of this type are not readily relieved by brief psychotherapeutic interviews And while I do not discard the importance of group psychotherapy, I believe that in most instances it is the individual approach to the individual patient that counts

Group psychotherapy is, in my opinion, a good preparation for the majority of patients for real psychotherapy, which can never be group psychotherapy Every individual is a distinct problem in itself I think Dr Gaskill will agree with me

Question Will you comment on the use of propylthiouracil, plus benzedrine-like substances such as used in cases of toxic goiter, in cases of depression?

DR YASKIN The only time I would consider the use of substances like benzedrine and dexedrine would be when we want to mobilize an otherwise markedly depressed patient Benzedrine is not going to make a depressed patient feel less depressed, but it will help the retarded patient so that he will be able, especially in the early hours of the morning to get around better and take care of his personal needs, or go to the shop and work And I believe that benzedrine, like good strong coffee, will do the trick, but it is not a good agent to use because of the constant fear that those who use it may commit suicide Gentlemen, I m not obsessed with suicide, it s a real thing even in mild depressions

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factors in the environment Unfortunately, psychotherapy is a tedious procedure and not every physician can become a psychiatrist any more than every physician can become a surgeon or roentgenologist

Question Dr Yaskin, what percentage of psychoneurotic patients are benefited by psychotherapy?

DR YASKIN I think that we can help patients under forty-five years of age to an appreciable extent, in about 60 per cent to 75 per cent of the cases There are some who cannot be helped at all because of the very nature of their psychoneurosis There may be just a tinge of schizophrenia which you sense Some of these patients are resistant and inaccessible

Unfortunately, psychotherapy is extremely time-consuming and for the majority of severe psychoneurotics, it is necessary to use the free association method If you do not use this method, after a few hours the patient and doctor alike are tired out and we do not get very far

ABDOMINAL SYMPTOMS OF ALLERGIC ORIGIN

MERLE M MILLER, M D

Allergy may be defined as a condition of unusual or exaggerated specific susceptibility or hypersensitiveness to a substance, usually a protein which is harmless in similar amounts for the majority of members of the same species Anatomically an allergic reaction causes edema of tissue, spasm of smooth muscle and increased capillary permeability of the part or organ involved Obviously such changes are quite capable of altering the function of the organ or system which is the seat of the allergic reaction The allergic state is inherited at least to the extent that the primary predisposition to hypersensitivity is transmissible

PATHOLOGY OF ALLERGY

The pathology of allergy is manifested by edema, increased capillary per meability, increased secretion of mucus spasm of smooth muscle, fibrinoid collagen degeneration, and eosinophilia, both local and general Any area of mucous membrane or skin may act as a shock organ for an allergic reaction, and certainly the whole pathology can occur anywhere in the gastrointestinal tract It is highly probable that injury to the epithelium of the gastrointestinal wall increases its permeability to proteins Experiments of Ratner and Gruehl indicate that the absorption of antigens is increased through damage to mucous membrane Primary antigens or unaltered foods or proteins usually can be incriminated in producing allergic edema, but proteoses amino acids histamine, histamine like substances and possibly nucleic acid, may be the etiologic agent The period of time which elapses from the time of absorption to the appearance of the allergic reaction varies from the instant of absorption to approximately thirty hours

There are three types of allergy that are recognized (1) spontaneous allergy, in which we usually find an hereditary background, (2) physiologic or ac quired allergy, and (3) contact allergy, which may be either spontaneous or acquired, but is usually the latter In most instances, acquired or physiologic allergy means that any normal person can be sensitized by repeated absorption of any particular antigen

In most instances, gastrointestinal allergy is an acquired type of allergy The blood serum of patients with spontaneous allergic manifestations usually contains a higher titer of skin sensitizing antibodies, while the serum in patients with acquired allergy usually contains no skin sensitizing antibodies, or they are in such quantity that a positive skin test reaction cannot be elicited

other gastrointestinal diseases, organic and functional should be eliminated before a diagnosis of allergy is made Favoring an allergic mechanism for abdominal symptoms acute or chronic, are varying combinations of the following findings (1) previous history of other allergic manifestations or a strongly positive family history (2) the presence of other allergic manifestations at the time of the attack (particularly urticaria angioneurotic edema nasal or bronchial symptoms migraine et cetera), (3) history of exposure to a known allergen (4) minimal physical findings in the presence of constitutional signs of shock (anaphylactic type)—rigidity is absent, muscle guarding is rare, rebound tenderness is usually absent and ordinarily tenderness is slight (5) presence of eosinophilia (6) absence of remarkable leukocytosis and neutrophilia, and (7) relief or marked amelioration of symptoms following an injection of epinephrine

TREATMENT OF GASTROINTESTINAL ALLERGY

At present we must be satisfied with the following therapeutic measures (1) elimination of known offending substances, (2) attempts at hyposensitization against these substances and (3) the use of drugs for temporary palliation All offending foods should be removed from the diet as soon as they have been identified One practical method of dealing with gastrointestinal allergy is the use of diversified diets In other words because of the quantitative as well as the qualitative action of specific proteins, the patient may be given a weekly menu which will diversify the foods in such a way that no food shall be repeated within four or five days Avoidance of a food for a period of time may make a patient less sensitive This procedure, diversified *diet may bring about some degree of hyposensitization except in some* patients who are highly sensitive to specific substances

Hyposensitization If symptoms persist after avoidance of offending foods, or if it is not practical to eliminate all substances to which there is reaction, hyposensitization may be attempted Successful results by oral desensitization have been reported by several observers The food is ingested in an unmodified state or as a pure protein allergen Usually the initial dose is a quantity somewhat less than that which gave a positive skin reaction The dose is gradually increased each day until the amount approximates that normally consumed The parenteral method of hyposensitization has also been tried in food allergy in much the same way as that employed with inhalants A few isolated reports mention some success with the procedure but in most instances it is attended with no better results than the use of the protein orally

SPECIFIC AND NONSPECIFIC REACTIONS It is interesting to note that as a result of hyposensitization of an allergic patient to an inhalant substance such as ragweed the patient may develop a certain amount of immunity to other pollens dust and inhalants It is possibly a sort of anamnestic reaction or a response the result of a specific nonspecific type phenomenon This may be the explanation for certain results obtained in the treatment of many allergic reactions It is certainly true that following the repeated entrance into the

Gastroscopy Changes attributed to allergy in some instances consist of distinct hyperemia, edema of the mucosal folds, and the presence of a grayish, tenacious mucus This procedure is done before and after the ingestion of a food that is suspected as the offending protein

Sigmoidoscopy This has been disappointing in most instances in patients suspected of having allergic colitis At the Graduate Hospital we were unable *to demonstrate a local eosinophilia* in mucus obtained from the lower bowel of patients suspected of having gastrointestinal allergy The same technic for staining was used as Hansel advises for nasal cytology

Roentgenographic Examination Special x ray studies may prove of benefit in the investigation of patients suspected of having gastrointestinal allergy Serial films should be taken before and after ingestion of barium, with and without the suspected antigen Barium enemas can be used, also with and without the antigen, to demonstrate by x-ray the changes that take place in the bowel during the allergic episode

Skin Tests If a positive reaction is elicited by the scratch test, using a 1 20 dilution of antigen, it is probable that the patient has some sensitivity to this protein In using the intracutaneous test, we sometimes get pseudoreactions, such as increase in the size of the wheal, pseudopod formation, and marked erythema We have found it helpful to repeat intracutaneous tests once or twice after the first positive reaction has been demonstrated, and if the reaction persists, then probably this test is correct In short, it is well to slightly overread scratch tests and underread intracutaneous tests The antigen used in intracutaneous testing is a 1 100 dilution for all preparations with the exception of cottonseed and egg white These two proteins are made up in a dilution of 1 10,000 or 1 1,000 If the Prausnitz-Kustner, or passive transfer, reaction can be evoked, a transfer of antibodies has been accomplished, and a positive test is confirmatory

Elimination Diets Many suggestions have been made as to the type of elimination diet to be used Rowe has published long and detailed elimination diets for use in a patient with suspected allergy Andresen has also reported special elimination diets A plan of procedure that can be followed is to allow the patient from six to twelve foods which are not normally in the diet If no reaction occurs, other groupings can be tried Another method is to start with one food and add, gradually, one food at a time, to the patient's diet The use of elimination diets in the diagnosis and treatment of allergy is sound, but obviously, no standard diet can be universally applied *If the elimination diet* can be correlated with the skin test, we have even more evidence of hypersensitivity The positive skin test does not mean that the patient is sensitive to this particular food If an allergic reaction occurs after the ingestion of a food to which the patient has reacted by skin test, this is confirmatory proof that he is hypersensitive to this protein

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of gastrointestinal allergy can be a long and involved procedure The most important point that must be kept in mind is that all

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body of certain protein substances, such as bacteria, the anamnestic reaction comes into force Ratner deals at length with the problem concerned in the harmful and beneficent responses of this phenomenon If an allergic person who had both hay fever and gastrointestinal allergy is desensitized to the offending inhalant allergens it is also possible that he receives a certain degree of hyposensitization to other substances, whether they be inhaled or ingested

Drugs If gastrointestinal symptoms are relieved by epinephrine hydro chloride they are possibly on an allergic basis For this reason, small doses of epinephrine can be given both for diagnosis and treatment Hypodermic injection of 0 5 to 1 0 cc of a 1 1000 dilution of epinephrine is indicated for the relief of acute severe attacks of abdominal allergy Relief is usually prompt Ephedrine may be valuable in gastrointestinal as well as in other types of allergy It is readily absorbed and may be given orally in the dose of 15 mg ($\frac{1}{4}$ grain) to 45 mg ($\frac{3}{4}$ grain) at intervals of every four hours until relief is obtained It has also been employed to abort attacks which appear periodically Propadrine hydrochloride, which has the same effect on the sympathetic nervous system as does ephedrine without the untoward side effects, may also be of value The advantage of this drug is that it can be given over a long period of time without producing the usual nervous effects attending ephedrine administration Often a capsule containing propadrine hydrochloride (24 mg, $\frac{3}{8}$ grain), atropine sulfate (0 2 mg, 1/300 grain), and phenobarbital (15 mg, $\frac{1}{4}$ grain) has proved successful in relieving the symptoms of an allergic reaction in the gastrointestinal tract A dose may be given three or four times daily

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barium sulfate and water was ingested by the patient Roentgenograms of the abdomen were taken after one two three and six hours Five or more days later the examination was repeated under identical circumstances except that the food to be studied was added to the opaque mixture As far as possible, the patients were kept unaware of the addition of the food The roentgenograms of both examinations were compared simultaneously, using an 8 light view box, in order to evaluate readily the comparative changes between the two examinations

Before the roentgen findings can be discussed, certain terms used in the description of the abnormalities must be defined

1 *Narrowing* Multiple areas of varying length of narrowing (below 1 5 cm) in the caliber of the small bowel

2 *Segmentation* Loss of continuity of the barium column due to breaking up into small boluses, separated by areas of narrowing

3 *Scattering* Quantities of barium of varying size retained in the ileum after the tail of the barium column has passed

4 *Transit Time* Time after swallowing required for the barium to reach the cecum

Group A FOOD HYPERSENSITIVE PATIENTS WITH GASTRO INTESTINAL MANIFESTATIONS

The foods tested in this group are shown in Table 18 It should be noted that 23 separate studies were performed although 20 patients comprised this group Three of the patients were sensitive to more than one food The results obtained are summarized in Table 19 The most striking changes in

Table 18 Foods Studied in Gastrointestinal Food Hypersensitive Group

FOOD	NO STUDIES
Milk	13
Egg	6
Pork	3
Corn	1
	23

this group were in the lower half of the small bowel Numerous areas of nar rowing were noted in all of the barium-allergen studies Segmentation occurred in all but one and scattering in all but two of the studies The transit time was abnormally rapid in six of the studies Six hour gastric retention emphasized in the literature, occurred in only four of the examinations None of these abnormalities was noted when barium and water alone were admin istered All of the patients in this group developed the symptoms which were noted in their histories when the barium-allergen mixture was used but were symptom free when barium and water alone was the opaque medium

ROENTGEN MANIFESTATIONS OF FOOD HYPERSENSITIVITY IN THE GASTROINTESTINAL TRACT

E J TALLANT, M D *

The first report of the roentgenographic examination of the gastrointestinal tract of a person suffering from food hypersensitivity was made by Halsknecht in 1906 [1] The offending food was mixed with bismuth and water and swallowed by the patient Antral spasm, gastric hypomotility and gastric retention were observed The next noteworthy contributions were by Weidemann (1921) and Urbach (1923) [3] Their principal findings were (1) spasm of the antrum with almost complete obstruction, (2) hypermotility of the body and fundus, (3) gastric retention and (4) hypersecretion Serio[4] was the first to compare the effects of food in sensitive and nonsensitive persons He found spasms of the stomach and intestines, hypomotility of the stomach and anti peristalsis in sensitive patients, while no abnormalities of pattern or motility were noted in the nonsensitive individuals Fries and coworkers[5] studied the changes in the gastrointestinal tract of a group of food-sensitive children and found gastric retention, increased or decreased gastric motility, occasional small intestinal hypermotility, some segmentation and scattering of the barium in the small intestine and spasm or dilatation of the colon Golden,[6] in 1941, after studying the small bowel pattern of a nurse hypersensitive to milk, felt that the changes which he observed when milk was in the opaque mixture were comparable to the typical abnormalities occurring in certain ' deficiency states ' Since that time, there have been several isolated reports of roentgenographic examinations of the gastrointestinal tract of food sensitive individuals

Because of a divergence in the descriptions of the changes occurring in the gastrointestinal tract of food sensitive persons, it was felt that a study of the problem under carefully controlled conditions would be of value

METHOD OF STUDY

Three groups of patients were studied

Group A Twenty patients with a history and clinical symptoms of food hypersensitivity of the gastrointestinal tract

Group B Eight nonallergic patients This group was studied to determine the effect of the foods themselves upon the normal gastrointestinal tract

Group C Six patients suffering from food hypersensitivity whose manifestations were not in the gastrointestinal tract

Identical procedures were used in all three groups After the food to be tested had been eliminated from the diet for at least five days, a mixture of

* The report is based upon the studies of Tallant, E J O Neill H Urbach F and Price A H

deficiency pattern which may occur in a variety of conditions The changes become specific when it can be demonstrated that they do not occur when barium and water alone are used

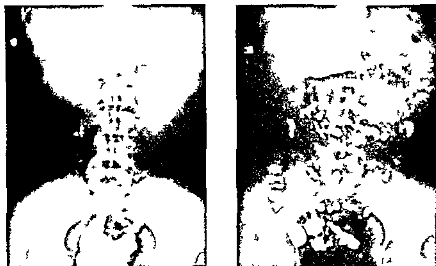


Fig 144 Three hour roentgenograms of patient (J S) hypersensitive to milk Left side—barium and water Right side—barium water and milk Narrowing segmentation and scattering on right side



Fig 145 Six hour roentgenograms of patient (J S) hypersensitive to milk Left side—barium and water Right side—barium water and milk Narrowing segmentation and scattering on right side but to lesser degree

In Fig 143 are the one hour roentgenograms of a twenty four year old veteran (J S) who had developed vague cramp like abdominal pains while

Two patients in this group had certain additional studies Foods to which they were not clinically sensitive were added to the opaque medium The roentgenograms obtained in this manner did not show the abnormalities noted when the offending food was administered The barium water allergen mixture was given to these two patients a second time and identical abnormal

Table 19 Roentgenographic Findings in Gastrointestinal Food Hypersensitive Group

ABNORMALITY	OPAQUE MIXTURE	
	Barium water	Barium water and Food
Mucosal pattern of stomach wide and edematous	0	2
Six hour gastric retention	0	4
Barium in cecum in one hour	0	6
Small bowel		
Narrowing	0	23
Segmentation	0	22
Scattering	0	21





Fig 143 One hour roentgenograms of patient (J S) hypersensitive to milk Left side—barium and water Right side—barium water and milk Narrowing segmentation and scattering on right side

ities were reproduced It may be inferred from this that the changes noted are specific in nature in that they occur only when the food to which the patient is sensitive is present in the intestinal tract It must be remembered, however, that the changes noted are not specific for food hypersensitivity but are a

Figure 145 shows the six hour films In the film on the right, the barium water milk study, the narrowing, segmentation and scattering although still present, are much less in degree While the barium-water milk examination was being performed the patient developed abdominal pain although he was unaware of the addition of the milk



Fig 147 Roentgenograms of patient (T K) hypersensitive to milk and egg Row A—barium and water Row B—barium water and milk Row C—barium water and egg Narrowing segmentation and scattering in Rows B and C

Figure 146 demonstrates the findings in a second patient of Group A This thirty-five year old woman (I H) had been sensitive to egg and pork since early childhood The ingestion of either of these foods resulted in the development of severe abdominal pain followed by nausea and vomiting The barium water study Row A, is normal (The numbers on the films denote the hour at which the films were obtained) In the barium-egg examination Row B there is widening of the rugal folds of the stomach, rapid transit time and narrowing segmentation and scattering of the barium in the ileum In the

in the Army After extensive investigation in an Army hospital he had been released from service with a diagnosis of psychoneurosis While attending the Veterans Psychiatric Out Patient Department of Jefferson Hospital, he was referred to the Medical Department for evaluation of his physical status We were fortunate in obtaining an indefinite history of an association between the



Fig 146 Roentgenograms of patient (I H) hypersensitive to egg and pork Row A—barium and water Row B—barium water and egg Row C—barium water and pork Narrowing segmentation and scattering in Rows B and C

abdominal symptoms and the ingestion of milk He was examined in the manner previously described

The film on the left side, the barium-water study, is normal That on the right, the barium water milk film, shows narrowing, segmentation and scattering

Figure 144 shows the three-hour films The changes present at one hour are still demonstrable

Figure 145 shows the six hour films In the film on the right, the barium water milk study, the narrowing, segmentation and scattering, although still present are much less in degree While the barium water milk examination was being performed the patient developed abdominal pain although he was unaware of the addition of the milk

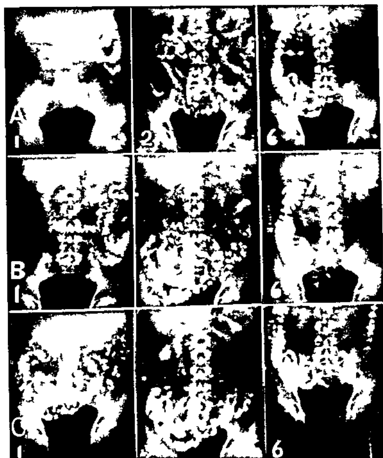


Fig 147 Roentgenograms of patient (T K.) hypersensitive to milk and egg Row A—barium and water Row B—barium water and milk Row C—barium water and egg Narrowing segmentation and scattering in Rows B and C

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barium pork study, Row C, the same changes are present In addition, six hour gastric retention occurred during the pork study During both the egg and pork studies the patient complained of abdominal pain

The final patient of Group A to be discussed is a forty two year old male (T K) who complained of abdominal distress and vomiting after breakfast, of four years' duration He discovered that the elimination of eggs from his breakfast would prevent the vomiting The abdominal distress persisted The ingestion of milk appeared to increase this distress The roentgenograms of this patient are shown in Fig 147 The barium water study, Row A, is normal In the barium milk examination, Row B, narrowing and segmenta



Fig 148 Roentgenograms of patient (H G) without sensitivity Row A—barium and water Row B—barium water and egg Rows A and B similar

tion are present in the ileum and the transit time was two hours In the barium egg examination, Row C there is narrowing segmentation and scattering in the ileum and the transit time was one hour During both the milk and egg examinations the patient experienced nausea and epigastric distress

Group B NON SENSITIVE PERSONS

Eight persons comprised Group B, the control group Patients attending the Surgical Out-Patient Department because of minor surgical conditions comprised this group Each of the four foods studied in the patients of Group A, milk, pork, egg and corn was studied in two members of this group The

barium-water and barium water food examinations were similar in all cases indicating that the foods, of themselves, did not produce the abnormalities noted in the study of the patients of Group A

Figure 148 illustrates the roentgenographic findings in a member of this group This patient (H G) had had a fractured right forearm and had returned to the clinic for the removal of the cast at the time the studies were instituted His history was entirely negative for any allergic manifestations Row A, the barium water study, and Row B, the barium water egg examination, are similar

Group C FOOD HYPERSENSITIVE GROUP WITHOUT GASTRO INTESTINAL DISTURBANCES

Six patients comprised Group C, those individuals whose abnormal reactions to food were not manifested in the gastrointestinal tract Two suffered from bronchial asthma, aggravated by the ingestion of milk, one from angioneurotic edema, provoked by eating peas, and the remaining three from neurodermatitis, two aggravated by chocolate and the third by milk There was no significant difference between the barium water and barium water allergen studies in any member of this group From this it may be concluded that the gastrointestinal tract must be the shock organ for the previously described roentgenographic changes to occur

Figure 149 illustrates the findings in a member of this group The patient a fifty two year old woman (A L) had suffered from seasonal bronchial asthma for thirty four years For the past ten years, the ingestion of milk had precipitated acute asthmatic attacks Row A the barium water study, and Row B, the barium water milk study, are similar

The question naturally arises, of what practical value is this roentgenographic method of demonstrating abnormalities in the small bowel of patients suffering from gastrointestinal food hypersensitivity? I agree with the preceding speaker, Dr Miller, that the diagnosis of food allergy must be based upon (1) a careful history, (2) close observation of the patient, and (3) the use of an elimination or modified elimination diet

The roentgenographic method of investigating food hypersensitivity should not be considered a routine diagnostic procedure As each suspected food would have to be individually tested the procedure is too time consuming and too complicated The procedure is an objective method applicable to the study of hypersensitivity it may be used to confirm a diagnosis obtained by the procedures outlined by Dr Miller It is primarily an investigational tool

RESULTS AFTER DESENSITIZATION

A brief description of one application of this procedure as an investigational tool will be presented during the remainder of the time allotted to me It will be necessary to make a few comments upon certain previous investigations Besredka[7] (1908) demonstrated that previous oral or hypodermic administration of minute sublethal quantities of anaphylactic substances gave temporary protection against otherwise uniformly occurring anaphylactic shock He was

able, completely and permanently, to eliminate anaphylactic shock by this treatment Dreyfus and Lesne[8] demonstrated that the administration of pre digested foods caused the loss of sensitizing and anaphylactic powers Luith len[9] found that the digestion of protein could be carried past the proteose level without loss of specificity and prepared type-specific protein digests E Urbach[10] stated that specific protein digests, which he termed Propeptans, when administered orally would produce permanent desensitization This statement was based upon animal experimentation and clinical results in hu mans We decided to observe what effect Propeptan desensitization would

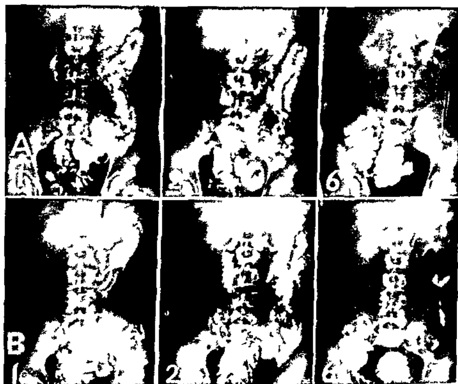


Fig 149 Roentgenograms of hypersensitive patient (A L) without gastrointestina manifestations Row A—barium and water Row B—barium water and milk Rows A and B similar

have upon the roentgenographic abnormalities demonstrated in the small bowel of the patients of Group A

Ten of the patients in Group A were selected and the procedure of Propeptan desensitization, as described by Urbach,[11] was carried to completion in these patients The patients were divided into two groups The first group, 7 patients, had no evidence of psychiatric disturbances while the second group, 3 patients, had longstanding psychiatric disturbances in addition to their food hypersensitivity This division was made as it has long been known[12] that psychiatric disturbances greatly accentuate allergic symptoms Following the period of desensitization, which required four to five weeks, all 10 patients

could ingest normal quantities of the previously offending foods without developing symptoms Roentgenographic studies of the gastrointestinal tract were then repeated, using barium, water and the food which had previously produced abnormalities as the opaque medium In all 10 patients, the small bowel pattern was similar to the original barium water study and did not show the changes which had occurred during the pretreatment barium water-

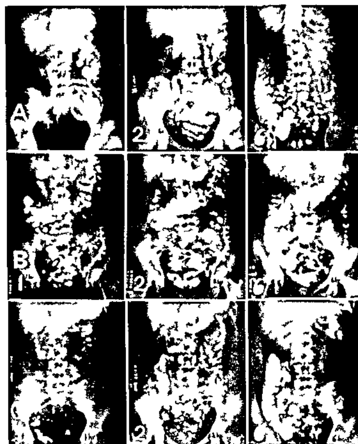


Fig 150 Roentgenograms of hypersensitive patient (I H) treated with Propeptans (Same patient as Fig 146) Row A—barium and water Row B—pretreatment barium water and egg Row C—post treatment barium water and egg The narrowing segmentation and scattering present in Row B is not present in Row C

allergen study The 3 patients with psychiatric disturbances clinically relapsed approximately six to eight weeks after the completion of treatment, while the 7 other patients have remained symptom free ingesting normal quantities of the previously offending food All 10 patients have been under observation for approximately ten months following the completion of treatment If one will accept the distinction made between the patients with psychiatric dis-

able, completely and permanently, to eliminate anaphylactic shock by this treatment Dreyfus and Lesne[8] demonstrated that the administration of pre digested foods caused the loss of sensitizing and anaphylactic powers Luith len[9] found that the digestion of protein could be carried past the proteose level without loss of specificity and prepared type-specific protein digests E Urbach[10] stated that specific protein digests, which he termed Propeptans, when administered orally would produce permanent desensitization This statement was based upon animal experimentation and clinical results in hu mans We decided to observe what effect Propeptan desensitization would

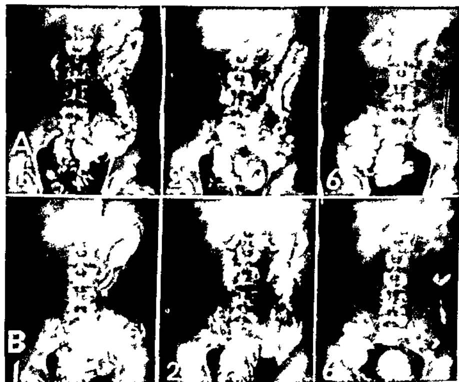


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SUMMARY

To summarize the opinions which we have formulated as a result of this study, the principal demonstrable changes occur in the small bowel and not the stomach of those individuals who suffer from gastrointestinal food hypersensitivity No changes were demonstrated in the gastrointestinal tract of the control subjects, showing that the foodstuffs themselves were not responsible for the changes No changes were demonstrated in those individuals whose allergic manifestations were not in the gastrointestinal tract. From this it may be inferred that the allergic reaction occurs between the antigen and the sessile antibodies in the shock organ and that other organs are not involved Interestingly enough no correlation was found between the skin tests and the roentgenographic findings although all patients were skin tested to the foods to which they were sensitive This may be due to one of two conditions either the skin due to the absence of sessile antibodies is not a shock organ or the patient may be sensitive to certain digestion products of the food and not be sensitive to the whole food This latter possibility is now being investigated and will we hope be the subject of a later report

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turbances and those without such disturbances, 100 per cent successful results were obtained in the nonpsychiatric group both clinically and roentgenographically If one will not accept such a distinction, 70 per cent successful results were obtained in the 10 patients treated These results were objectively demonstrated and did not depend upon the subjective response of the patient, thus showing one application of the procedure under discussion

Figures 150 and 151 illustrate the results obtained by the use of Propeptan therapy The original studies of this patient (I H) were previously discussed (Fig 146) In Fig 150 Row A is the pretreatment barium water

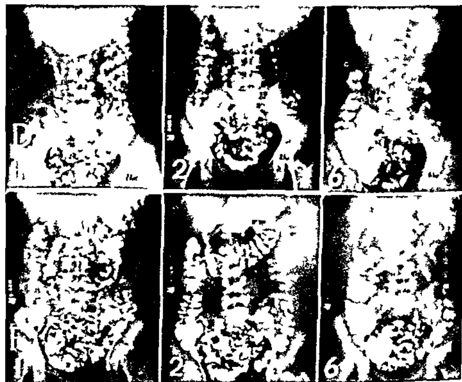


Fig 151 Roentgenograms of hypersensitive patient (I H) treated with Propeptans (Same patient as Fig 146) Row D—pretreatment barium water and pork Row E—post treatment barium water and pork The narrowing segmentation and scattering in Row D is not present in Row E

study, Row B, the pretreatment barium-water-egg study, and Row C, the post-treatment barium-water-egg study It will be noted that the narrowing, segmentation and scattering demonstrated in Row B are not present in Row C although egg was present in both studies Row D of Fig 151 is the pretreatment barium-water pork study and Row E the post treatment barium-water pork study It will again be noted that the narrowing, segmentation and scattering present before treatment are not demonstrated after treatment This patient has remained symptom free for the past ten months, ingesting normal quantities of egg and pork

SUMMARY

To summarize the opinions which we have formulated as a result of this study, the principal demonstrable changes occur in the small bowel and not the stomach of those individuals who suffer from gastrointestinal food hypersensitivity No changes were demonstrated in the gastrointestinal tract of the control subjects, showing that the foodstuffs themselves were not responsible for the changes No changes were demonstrated in those individuals whose allergic manifestations were not in the gastrointestinal tract From this it may be inferred that the allergic reaction occurs between the antigen and the sessile antibodies in the shock organ and that other organs are not involved Interestingly enough no correlation was found between the skin tests and the roentgenographic findings although all patients were skin tested to the foods to which they were sensitive This may be due to one of two conditions either the skin due to the absence of sessile antibodies, is not a shock organ or the patient may be sensitive to certain digestion products of the food and not be sensitive to the whole food This latter possibility is now being investigated and will we hope, be the subject of a later report

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AN APPRAISAL OF ABDOMINAL SYMPTOMS OF ENDOCRINAL ORIGIN

ABRAHAM E RAKOFF, M D

Abdominal and gastrointestinal symptoms are not prominent manifestations of many endocrine disorders On the other hand, such symptoms often occur as part of the picture in certain endocrine dysfunctions, particularly those of the thyroid and the ovary However, for the sake of completeness, I should like to review very briefly those gastrointestinal and abdominal manifestations which may occur in disturbances relating to the other endocrine glands before discussing the thyroid and ovary in more detail

THE ANTERIOR PITUITARY

In pan-hypofunction of the anterior pituitary, as in Simmonds' disease, the gastrointestinal manifestations are chiefly those due to cachexia and anorexia In this respect, I would like to point out that testosterone has proved to be of great help in combatting both the anorexia and weight loss, it has been more effective than pituitary replacement therapy because of the inadequacy of our present whole pituitary preparations In less marked disturbances of the pituitary, such, for instance, as Frohlich's syndrome, which arises from a disturbance in the hypothalamus, the gastrointestinal manifestations and abdominal symptoms are those which are related to the obesity and disturbance in appetite and water regulation In hyperfunction of the pituitary, such as in the syndrome of acromegaly, abdominal manifestations may be related to the splanchnomegaly which is observed in the latter condition It is said that the enlargement of the abdominal organs in acromegaly is out of proportion to the increase in the size of other organs In gigantism, on the other hand, the abdominal organs increase in proportion to the increase in the size of the skeleton In basophilic adenomas of the anterior pituitary producing a Cushing's syndrome, disorders relating to the abdominal organs are those which are incident to the trunk obesity, osteoporosis of the spine and to the diabetes which may occur in this condition

THE PARATHYROIDS

Hypofunction of the parathyroids with resultant tetany may produce those gastrointestinal manifestations which result from heightened neuromuscular dysfunction such as difficulty in deglutition, increased or abnormal peristalsis and sometimes abdominal pain and persistent vomiting In hyperfunction of the parathyroids, constipation is a common manifestation, while nausea, vomiting and anorexia are also frequent symptoms Gastritis is also common and gastrointestinal hemorrhages have been produced experimentally by injection of large amounts of parathyroid hormone

THE ADRENAL

In hypofunction of the adrenal cortex such as occurs in Addison s disease or in less severe states of adrenal cortical insufficiency, anorexia is of course the chief gastrointestinal manifestation Sometimes associated with it are nausea and constipation Hyperfunction of the adrenal cortex rarely produces any important gastrointestinal or abdominal symptoms In hyperfunction of the adrenal medulla, however, as seen in patients with a pheochromocytoma, abdominal symptoms are common in that during the attack crises of abdominal pain may be noted Hemorrhages in the gastrointestinal mucosa are also frequently found

THE THYROID

In thyroid hypofunction anorexia and constipation are important and common symptoms The anorexia is said to be due to the diminished need for intake of food and constipation results from diminished abdominal peristalsis Constipation is estimated to be present and to be an important symptom in about three fourths of the cases of marked hypothyroidism In children, particularly, constipation may be the prime manifestation and the one which may lead to a very early diagnosis before other manifestations make themselves apparent Occasionally tympanites may be a troublesome symptom Several cases of hypothyroidism have been reported by Means, for instance, in which tympanites was the outstanding manifestation and in fact responded to thyroid extract Achlorhydria has been found by Means and Lerman to occur in 53 per cent of hypothyroid patients

In thyroid hyperfunction particularly in toxic goiter, increase of appetite is noted early and loosened bowel function is a common manifestation In patients who have always been constipated, one of the earliest changes noted with increase in basal metabolic rate is the change to normal bowel movements, while in patients with normal bowel function all their lives, the onset of frequent bowel movements or diarrhea occurs as toxicity increases Achlorhydria is also said to be common in hyperthyroidism, occurring in 38 per cent of Means group Nausea and vomiting are not common in toxic goiter, and when they do occur are generally serious manifestations occurring late in the disease and in association with severe toxicity

THE TESTES

In testicular dysfunctions, abdominal symptoms are uncommon unless associated with some mechanical factor For instance, in cryptorchidism there may be pain associated when the testis is in the process of descent, but otherwise gastrointestinal symptoms are not a common manifestation of testicular deficiency states

THE OVARIES

On the other hand in dysfunctions of the ovary, abdominal symptoms are of common occurrence These appear not only in dysfunction but also to some degree in association with the normal cyclic function of the ovary

During the normal menstrual cycle, as the *follicle grows and the estrogen* production increases as the mid-cycle is approached, it is common to have patients complain of lower abdominal fullness, distention, tenderness and many of the manifestations which have been attributed to pelvic congestion Sometimes the act of ovulation itself is associated with varying degrees of pain This pain is usually unilateral and may occur in the region of iliac crest or more posteriorly, frequently it radiates downward toward the leg and is often associated with abdominal distention When the pain occurs to a more severe degree, it is spoken of as "mittelschmerz" and may simulate that due to serious intra-abdominal lesions such as acute appendicitis or a ruptured ectopic pregnancy Occasionally the release of the ovum is followed also by bleeding from the corpus haemorrhagicum Such oophoragia due to a ruptured follicle has in some instances led to operation for an acute abdominal condition

After ovulation has occurred, there may result a new train of abdominal symptoms due to the release of the second ovarian hormone, *progesterone* Progesterone, probably more than any one other hormone, is a gastrointestinal "irritant" *in the sense that it increases nervous tension and produces* pelvic congestion As a result abdominal symptoms, particularly in the form of distention, occur during the last half of the cycle as a common normal manifestation Some patients can tell that their menstrual period is soon due because of the onset of constipation On the other hand there are some patients, particularly those women who develop a marked degree of pre*menstrual tension with marked* nervous irritability, *who develop diarrhea in* the premenstrual phase which may last through the first or second day of the menstrual flow During the premenstrual phase an extreme degree of "tension" may develop in some individuals and this syndrome is spoken of as a state of "premenstrual tension" It is characterized by not only heightened nervous irritability generally, but personality changes, retention of fluid, mastalgia and marked abdominal distention with changes in bowel function either towards constipation or diarrhea Cramps may also begin during this phase and in some patients moderate cramps may be present all during the progesteronic phase followed by severe dysmenorrhea at the time of the onset of the menstrual flow

The pain at the onset of the menstrual flow in many young women becomes sufficiently great to be spoken of as *dysmenorrhea* Dysmenorrhea is generally believed to be due to exaggerated uterine contractions, although diminished threshold of pain also plays an important part The causes of dysmenorrhea are not fully known, and a great many etiologic factors have been postulated, for instance, a cervical canal which is not sufficiently patent, hypoplasia of the uterus itself, neuritis of the presacral nerves, increased pelvic congestion pressing upon the pelvic nerves and finally, endocrine factors as well as psychic factors That endocrine factors probably play an important part in dysmenorrhea is evidenced by the remarkable relief which one can get by inhibiting ovulation Dysmenorrhea seems to be a disease of the normal cycle It very rarely occurs in the presence of menstrual abnormalities, or in anovu

latory cycles Therefore if one can "knock out ovulation one frequently can help dysmenorrhea with its many associated manifestations For instance giving sufficient estrogen early in the cycle will depress the anterior pituitary and prevent ovulation This is now used as a therapeutic test to determine whether the dysmenorrhea is primary, that is not associated with any pelvic abnormalities If the patient goes through a perfectly normal menstrual period free of any pain free of premenstrual tension and dysmenorrhea then the disease is believed to be of primary origin and not associated with any organic lesion in the pelvis Unfortunately, however, this type of therapy cannot be long continued in young women because it means inhibiting the pituitary and ovaries and inhibiting fertility Another approach therefore, is to use testosterone during the last half of the cycle because it is believed that in these patients the high titer of estrogen as well as progesterone may be a factor Testosterone tends to inhibit the effect of both of these hormones on the uterus, but the results with testosterone are not dramatic Progesterone, which is spoken of as a uterine sedative and which ought to diminish uterine contractions, is not helpful in the treatment of most cases of dysmenorrhea and in some cases may even make the dysmenorrhea more severe

In many dysmenorrheic patients nausea and vomiting become an important manifestation and some of them may go on to vomit and lose weight over a period of a whole week so that in the postmenstrual phase they may be in very poor condition

I should like to point out also the importance of the progesteronic phase in patients who already have some gastrointestinal condition patients with colitis patients with ulcers and patients with various gastrointestinal diseases that are made worse by a heightened state of nervous irritability produced by progesterone Therefore the use of methods temporarily or over a long period of time to abolish this phase of the cycle may under certain circumstances be necessary and worth while in the treatment of severe gastrointestinal dys functions

During *pregnancy* the nausea and vomiting which occur in early pregnancy, and the hyperperistalsis which is noted in some patients, is also believed to be due to an increase in both the estrogen and progesterone content, and as a matter of fact these are the same symptoms which may be produced in nonpregnant individuals by hyperestrogenism after giving large amounts of any estrogen but particularly the synthetic estrogens

Pseudo pregnancy is an interesting condition because among its manifestations is marked enlargement of the abdomen usually due to marked distention This is believed to be due to persistence of the corpus luteum on a psychic basis The belief or fear that the patient may be pregnant may indirectly release enough luteotrophin from the pituitary to cause the corpus luteum to persist and produce estrogen and progesterone The latter is believed to lead to the gastrointestinal manifestations, i e abdominal distention and sometimes fetal movement which are noted in these patients

At the *menopause* gastrointestinal manifestations and abdominal symptoms are relatively minor because although there is heightened nervous irritability,

there is also a diminution in the ovarian factor As the patient approaches the menopause, ovulation goes first, and then both progesterone and estrogen diminish so that dysmenorrhea, ovulatory pains and the premenstrual train of gastrointestinal symptoms disappear

PANEL DISCUSSION

Question What is the dosage of the sex hormones used?

DR RAKOFF In the patients that I spoke of with pituitary cachexia in the male, or in men with wasting diseases of gastrointestinal origin where it is desired to increase weight and improve appetite, testosterone is very well tolerated and should be given in large dosage for best effects, such as 75 mg of testosterone propionate by injection three times a week for the first month and then reduced to 50 mg Later on a pellet can be implanted if necessary, and if pellets are used four pellets of 75 mg each are implanted in the subscapular area every four months These are of particular use, however, in true endocrine dysfunctions

In females testosterone is not as well tolerated and must be given cautiously if arrhenomimetic effects are to be avoided It is generally possible to obtain a good result by mouth using methyl testosterone in 10 mg tablets One can start by giving 20 mg of methyl testosterone daily until the skin becomes oily, which is usually the first symptom of overdosage, and then cut to 10 mg a day In the treatment of dysmenorrhea to inhibit ovulation which is done, as I pointed out before, only as a temporary measure one may give estrogen in the form of stilbestrol, 1 mg daily, or premarin, which is a natural estrogen, in a dosage of 2 5 mg daily starting right after the menstrual period is over and stopping five days before the patient is due again For the relief of pre menstrual tension and its associated phenomena methyl testosterone may be given in a dosage of 10 mg a day from the fourteenth to the twenty fourth day of the cycle In other words, you begin two weeks before the patient expects her period and stop about four days before the menstrual flow is due

Question In a female age thirty four, one ovary removed due to chocolate cyst, which I presume was meant to be endometriosis, who has severe pains for two weeks before the onset of menses, what is the best therapy?

DR RAKOFF First one has to anticipate the possibility of recurrence of the endometriosis On the other hand, this might not be the case and it might possibly be on the basis of a syndrome of premenstrual function and dys menorrhea In either event, I think that therapy with testosterone, provided the physical findings fail to indicate any evidence of recurrence, would be worth while, and for this purpose testosterone would probably have to be

given during the first two months through the cycle in order to get good inhibition of the entire cycle One could give 10 mg of methyl testosterone right through the cycle for one, two or three months, long enough to actually inhibit the whole cycle and prevent menstruation After that one then could reduce the dosage and give it only in the premenstrual phase

Symposium on The Pancreas

that the several enzymes are secreted in parallel concentration, that is, an increase in the concentration of one enzyme is accompanied by a proportionate increase in all the others So far as I know, mechanical stimulation of the gastric or duodenal mucosa is not mentioned in the literature as an effective stimulus for the pancreas

In contrast to other digestive glands, the pancreas apparently has only one type of secreting cell The secretion is, nevertheless, complex and variable, so it is necessary with our present knowledge to assume that the single acinous cell is capable at one time of secreting a fluid with a high enzyme content and a minimum of bicarbonate, and at another time of secreting bicarbonate and water with a minimum of enzymes Still more remarkably it is able to vary the relative concentration of these two classes of components over a wide range of response to a great variety of stimuli

I propose in this discussion to point out some of the less certain aspects of this classic picture and to present some experimental evidence which seems to warrant their reinvestigation The first concerns the relative importance of hydrochloric acid as a stimulus for the normal intestinal phase during digestion

HYDROCHLORIC ACID AS A STIMULUS FOR PANCREATIC SECRETION

In order to serve as a stimulus for pancreatic secretion, the intestinal contents must contain an effective concentration of acid In order to determine whether effective concentrations are in fact present during digestion, one must know first what concentrations are effective, and second, the actual concentrations of acid to be found in the intestine during digestion Dr Crider and I[2] at one time attempted to make these essential measurements We found the threshold for pancreatic stimulation to range from pH 3 0 to pH 5 0, depending on the acid used The property of the acid most important for effective stimulation at a given pH appeared to be its buffering capacity Considering the buffering capacity of the intestinal contents, we judged that they would have a minimal effect at about pH 4 0 Our own measurements of intestinal acidity agreed with many others, that a pH of 4 0 is a fairly common occurrence in the duodenum

Figure 152 presents a curve[3] showing the distribution of some 210 samples of duodenal contents collected from a dog after a meal of raw meat, and you see a majority of the samples had a pH near 4 0, the total range is from 2 8 to 5 2 Meat was selected for this study because we had observed that meat produced a more acid intestinal content than any of the other foods that we had tried

Figure 153 shows a study made by Dr Berk[4] also on dogs, in which instead of meat a carbohydrate meal was used The black columns show the distribution of samples from the duodenum, it is evident that the intestinal contents are less acid after the Ewald meal than after meat

Figure 154 is also taken from one of Dr Berk's papers[5] and shows the same sort of observations with the same type of meal in human subjects Again

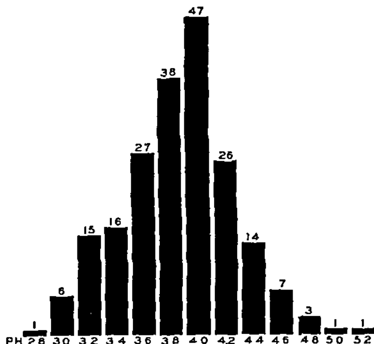


Fig 152 Distribution with respect to pH of samples collected from the first part of the duodenum The height of each column is proportional to the number of samples having the reaction indicated in pH units at the bottom of the column. The number of samples is indicated at the top of each column (Thomas in Am J Digest Dis Vol 7 1940)

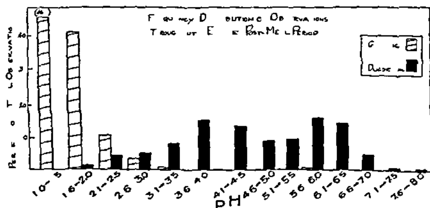


Fig 153 Acidity in pH units of samples collected simultaneously from just above and just below the pylorus Only the black columns refer to samples obtained from the duodenum (Berk Thomas and Rehfuss in Am J Physiol Vol 136 1942)

although some of these samples tend to be more acid than those in the dog, they show a distribution around pH 5 0 this being about the center of the

curve, although there is a double hump which we do not understand Those of you who were here yesterday will remember that Dr Berk showed some pH determinations in ulcer patients after a meal of milk and cream and in those the acidities were very much lower than these which were obtained after an Ewald meal I asked Dr Berk about that this morning, and he is unable to explain the difference, except that he has the feeling that in ulcer patients the acidity tends to be lower than in the normal That, of course, does not concern our problem which is normal physiology

So far the experimental evidence does not exclude acid as an important stimulus for pancreatic secretion However, some other foods produce a less acid intestinal content, notably fats, they do, nevertheless, adequately stimulate the pancreas Furthermore, some clinical investigators[6, 7] have pointed out that pancreatic secretion appears to be adequate in achlorhydria—at least

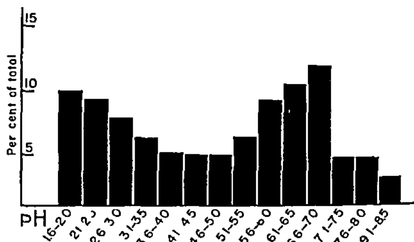


Fig 154 Redrawn from data published by Berk[6] Acidity in pH units of samples collected from just beyond the pylorus in normal human subjects after an Ewald meal Distribution is shown in terms of per cent of total number of samples having the pH range indicated below each column

with respect to enzymes These considerations prompted further investigation

Dr Pincus and his coworkers[8] at the Jefferson Medical College undertook a direct approach to the problem They measured the volume of pancreatic juice secreted by dogs during measured time intervals while the animals were digesting various types of meals and determined the pH of samples of intestinal contents collected during the same time intervals They found, as have others, that both the volume of pancreatic juice and the intestinal pH varied from moment to moment through a considerable range They confidently expected to find that these fluctuations would be related to each other in such a way that an increase in volume in pancreatic juice would be associated with an increase in intestinal acidity and vice versa This did, in fact, happen on occasion, but just as often the volume increased while the acidity decreased, or the two showed no recognizable relationship whatever

Figure 155 shows the assembled data, volume as plotted on the abscissas and pH on the ordinates, you see that there is a wide scatter with no definite trend, there may be just a very slight tendency for the pH values to be lower when the volume is very high, but not enough to establish a correlation

We are well aware of the fact that the intestinal contents are not a homogeneous mixture and the pH of a sample collected at one point may not be representative of the whole This source of error, if it is important, should be more apparent in the individual experiments than in the data as a whole In this study there was good agreement between the individual experiments and the assembled data There are other defects in the evidence, possibly, but I do not wish to be argumentative, I merely wish to point out that efforts to confirm the classic hypothesis experimentally have not been successful We

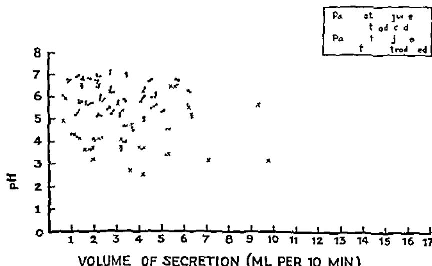


Fig 155 Scattergram showing the relationship between the pH of the duodenal content and the volume of pancreatic juice secreted during the ensuing ten minute period (Pincus et al in Proc Soc Exper Biol & Med 1948)

think this is sufficient to raise a reasonable doubt as to the validity of the classical viewpoint particularly since it is based on an hypothesis only and not on experimental evidence

THE PARALLEL SECRETION OF ENZYMES

The next question that I wish to raise concerns the parallel secretion of enzymes i e the hypothesis advanced by Babkin[1] that an *increase or decrease* in the concentration of one enzyme is accompanied by a corresponding change in the concentration of all other enzymes Numerous clinical observations, especially those of Comfort and Osterberg[9] in this country, as well as some studies by Christiansen[10] confirmed by Lagerlof[11] in Europe do not support this hypothesis In 1943 Grossman and Ivy[1] reported a study *on rats which*

seemed to show that the relative concentration of various enzymes in pancreatic tissue was not constant but varied with the diet Dr Beamer in our laboratory has tried similar experiments using dogs instead of rats and pancreatic juice instead of pancreatic tissue Not only did he find variations in average relative enzyme concentration, possibly associated with change of diet, but he was unable to verify parallel secretion of enzymes in animals on a constant diet In these experiments pancreatic juice was collected in the intervals between meals after administering hydrochloric acid into the duodenum Trypsin, amylase and lipase were determined daily Considerable fluctuation in the concentration of each of these enzymes was observed from day to day The variations in concentration of each enzyme were frequently unrelated to variations in concentration of other enzymes The whole picture was one of random variation without evidence of parallelism

In a discussion of these results with Dr Babkin he criticized the method inasmuch as we used hydrochloric acid which does not specifically stimulate the secretion of enzymes by the pancreas, I think his criticism is possibly valid We hope to repeat these observations using pancreozymin, if Dr Friedman is able to prepare pancreozymin for us—something he has not succeeded in doing as yet

CELLULAR SOURCE OF SECRETION

Another problem has to do with the source within the pancreas of the different constituents of the secretion, specifically the enzymes on the one hand and the fluid and bicarbonate on the other As I said before, because the pancreas apparently possesses only one type of secreting cell, it has been assumed that the fluid, bicarbonate and enzymes were all produced by the same type of cell Recent work by Lagerlof[11] and by Friedman and Snape[13] has shown that in pancreatic disease the secretion of enzymes may be suppressed, while the secretion of fluid remains normal or nearly so This suggests that two different tissues may be involved in these functions The characteristic pancreatic enzymes obviously come from the acinous cells, but where is the fluid secreted?

A study by Grossman and Ivy[14] of the effects of alloxan on the pancreas suggests that the fluid may be secreted by the cells of the intralobular ducts They found that in alloxan treated dogs in addition to the well known damage to the islet tissue, the cells of the intralobular ducts showed vacuolization, at the same time there was a suppression of the secretion of fluid as indicated by an increase in the amount of secretin required to initiate secretion Enzymes remained normal

In another study from Ivy s laboratory[15] it was found that pancreozymin, which increases the output of digestive enzymes from the pancreas, did not augment the output of alkaline phosphatase Another observation made in the same study was that the phosphatase apparently was localized in the cells of the intralobular ducts, again implicating these ducts as being the source of certain constituents of the pancreatic juice

MECHANICAL STIMULATION BY THE DUODENUM

Finally I should like to raise a question regarding the possible influence of mechanical stimulation of the duodenum on pancreatic secretion This subject appears to have been neglected by physiologists inasmuch as no mention of it occurs in the literature so far as we can find up to the present Nevertheless *it is a matter of some consequence because of the practice of intubating the* stomach and duodenum in studies of pancreatic function

Dr Waldron of the Jefferson staff in physiology became interested in the effects of tubes in the duodenum in connection with a study of pancreatic function in fistula dogs In the arrangement used by Dr Waldron there are two tubes entering the stomach by way of the gastric fistula and passing through the pylorus into the duodenum This produces a situation comparable to that obtained when a tube is passed by mouth and is allowed to enter the duodenum Briefly stated his results indicate that in a majority of dogs tubes in the duodenum increase the fasting secretion of the pancreas, or initiate secretion if the pancreas is not already secreting On the other hand such mechanical stimuli tend to suppress somewhat the response to food

These studies have been checked to determine whether the effect was due to incidental conditions other than mechanical stimulation, the rubber in the tubes for instance Other mechanical stimuli such as stuffing cotton into the intestine have the same sort of effect as the rubber tube, so it isn t just a case of chemical action of rubber other controls were used which seemed to indicate that the effect is really a result of mechanical stimulation

One animal gave results that were exactly the opposite of those described, therefore we must study more animals The explanation that we have offered for the contradictory results on this animal is that he was perhaps, hypersensitive to mechanical stimulation we know as a matter of general experience that very strong mechanical stimulation causes inhibition of many functions including pancreatic secretion

The first effect, i e , stimulation during the fasting period is doubtless a direct effect on the duodenal mechanism responsible for pancreatic secretion but the inhibition late in digestion is probably an indirect influence acting through the effect of the tubes on gastric emptying These studies are preliminary and not all dogs behave alike but enough information is at hand to prove beyond a reasonable doubt that mechanical stimuli influence pancreatic secretion, either to augment or inhibit it Probably mild stimuli such as are associated with the presence of the duodenal contents will prove to be excitatory whereas strong or noxious stimuli are inhibitory but these are problems for the future

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What are the mechanisms that would cause a complete or partial block of the main pancreatic duct? (1) Pancreatic stones or inspissated intraluminal contents, (2) intramural swellings due to inflammation or tumor of the main pancreatic duct (3) extraluminal pressure on the main pancreatic duct in most instances due to inflammation or tumor, either in or adjacent to the pancreas Any of these processes that tend to occlude the passage of contents in the main pancreatic duct may give rise to an elevation in the serum enzymes in the blood Elevated serum amylase and lipase values merely reflect the fact of increased intraluminal pancreatic duct pressure without reference to what might be the primary cause in the pancreas itself

In the next paper, Dr Raffensperger is going to discuss with you some instances in which the primary cause of the elevated serum enzyme values lay outside of the pancreas, but in which usually there could be demonstrated or inferred some secondary effect of compression of the main pancreatic duct

The normal values of the serum lipase test are below 1 0 cc of twentieth-normal sodium hydroxide, using the modified Cherry and Crandall technic Some laboratories accept normal values up to 1 5 cc of twentieth normal sodium hydroxide Technical limitations of the test preclude assigning any significance to low values as evidence of decreased pancreatic function The serum lipase test requires a twenty four hour period of incubation before completion The serum amylase may be reported within an hour Therefore the serum amylase may be available at the time when it is of the utmost importance to the clinician in attempting to diagnose an early case of severe upper abdominal disease

The normal values of the serum amylase test using the Somogyi technic are below 125 mg of glucose As with serum lipase, low values cannot be regarded as evidence of decreased pancreatic function

CLINICAL MATERIAL

In Fig 156 we have illustrated the serum lipase values in two cases of acute pancreatitis Case M F (solid line) had an initial value of 8 0 cc of N/20 sodium hydroxide Five days later the value was below 1 0 cc and the patient was well Case T V (dotted line) had an initial value of over 4 0 cc, but on the day of death seven days later the serum lipase approached zero Case M F had acute transient edema of the pancreas which promptly subsided in five days Case T V had acute hemorrhagic pancreatic necrosis with autopsy confirmation In both instances the initial pathologic process caused compression of the main pancreatic duct which was reflected in an elevation of the serum lipase, illustrating the fact that the elevation in the serum lipase value merely reflects the presence of compression of the main pancreatic duct without reference to the exact mechanism The latter must be determined on the basis of an evaluation of the whole clinical picture The low value of the serum lipase in case T V seems related to extensive or almost complete pancreatic destruction in which there is no tissue remaining capable of forming lipase

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VALUE OF SERUM AMYLASE AND LIPASE DETERMINATIONS IN THE DIAGNOSIS OF PANCREATIC LESIONS

THOMAS A JOHNSON, M D

For many years it has been evident that a simple type of laboratory test was needed for a proper evaluation of pancreatic lesions As the result of a great deal of work by many investigators, attention has been focussed on the serum lipase and the serum amylase The practical advantage of taking a specimen of blood and, with relatively simple technics, arriving at conclusions regarding the enzymes in the blood, is a considerable improvement over the rather cumbersome technics and generally unreliable results that were obtained in the past with the use of tests on the urine or feces

A great deal of experimental pancreatic study has been done using duodenal intubations such as Dr Thomas described It is obvious that such determinations are of extreme value in a study of the physiology of the pancreas, but they are of limited value in the patient with acute illness Serum amylase and lipase normally are present in the blood in fairly definite concentrations

I shall not discuss the technic for the determination of serum amylase and lipase The technic in each case is simple laboratory procedure that is well adapted to the office and certainly to any hospital

RATIONALE OF THE SERUM AMYLASE AND LIPASE DETERMINATIONS

Any mechanism which tends to block the normal egress of pancreatic juice from the main pancreatic duct into the duodenum may be reflected in an elevation of the serum amylase and lipase We have no practical test for estimating trypsin in the blood

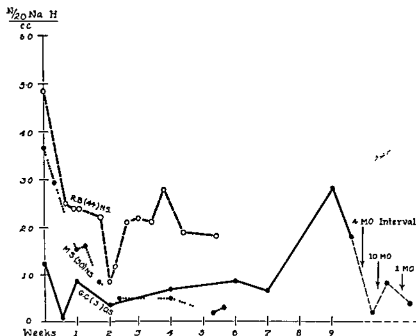


Fig 157 Serial determinations of serum lipase over a period of several weeks in 3 cases of acute pancreatitis

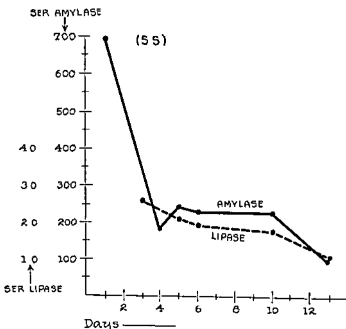


Fig 158 Behavior of serum amylase and lipase in 2 cases of acute pancreatitis

Figure 157 illustrates three cases of acute pancreatitis, each of which was studied by serial determinations of the serum lipase values over a period of a number of weeks Case G C (solid line) illustrates a recrudescence of the disease over two months after the onset We lost sight of case R. B before the serum lipase value returned to the normal level

Figure 158 also illustrates a case of acute pancreatitis The initial value for the serum amylase was 700 mg, which fell to below 200 mg on the fourth day of the disease The decrease in the values of the serum lipase occurred

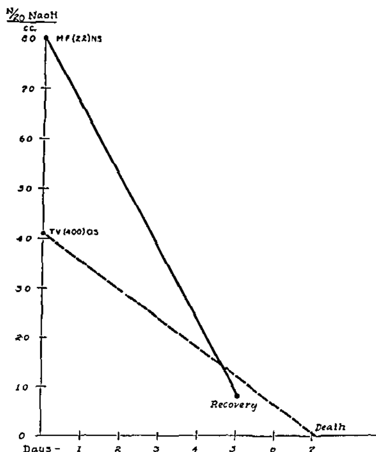


Fig 156 Serum lipase values in two cases of acute pancreatitis

at a somewhat more deliberate pace In our experience in acute pancreatitis the serum amylase values are more labile and seem to reflect rapid changes in the disease process to a more satisfactory degree than does the serum lipase In the more prolonged block of the main pancreatic duct seen in carcinoma of the head of the pancreas, the serum lipase is the more satisfactory of the two tests We have found that a stat serum amylase determination is indis pensable in the differential diagnosis of acute upper abdominal conditions in which acute pancreatitis must be ruled out

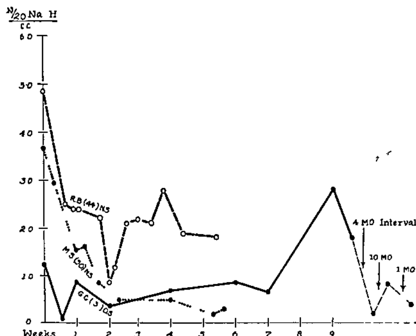


Fig 157 Serial determinations of serum lipase over a period of several weeks in 3 cases of acute pancreatitis

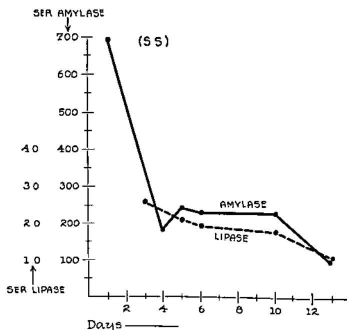


Fig 158 Behavior of serum amylase and lipase in 2 cases of acute pancreatitis

Figure 159 illustrates serial determinations of serum lipase values in three cases of carcinoma of the pancreas, each of which was followed to necropsy This figure demonstrates a number of important aspects of the interpretation of the serum lipase in instances of carcinoma of the pancreas As with inflammatory changes in the head of the pancreas, the elevated serum lipase value is related to pressure on the main pancreatic duct but due in this instance to the influence of a growing tumor in juxtaposition to the main pancreatic duct In case A B (solid line) the initial value of 5 0 cc. N/20 sodium hydroxide gradually fell to within the normal range of less than 1 0 cc at the time of death At necropsy almost the entire pancreas had been replaced by tumor tissue, hence there was a progressive decrease in the amount of functioning pancreatic tissue which was reflected in decreased serum lipase values A single normal serum lipase determination shortly

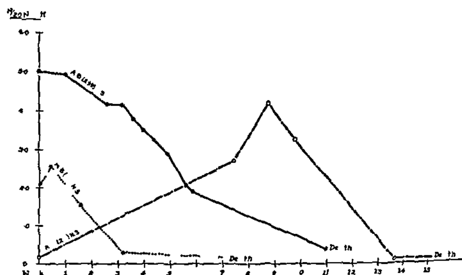


Fig 159 Serial determinations of serum lipase in 3 proved instances of carcinoma of the pancreas

before death in such a case gives an erroneous concept of the nature of the disease process In a series of cases of carcinoma of the pancreas, an elevated serum lipase value will be obtained in only 40 per cent of the cases, due largely to the fact that the case is already in an advanced stage at the time of the initial admission to the hospital Case A L (broken line) was picked up with an initial normal serum lipase value at a time when we were doing serum lipase determinations on all out patients merely to determine the specificity of the test in pancreatic cases Case A L had a duodenal roentgen defect erroneously attributed to a benign duodenal ulcer Seven weeks later, he reappeared with mild jaundice and a serum lipase of 2 7 cc was recorded At operation and subsequent necropsy, the diagnosis of carcinoma of the pancreas was established In case A L we can follow the serum lipase through from a time prior to compression of the main pancreatic duct, through the period of compression on the duct in the presence of functioning pancreatic

tissue and its final phase in which complete replacement of functioning pancreatic tissue by adenocarcinoma was reflected in a serum lipase value within the normal range about ten days prior to death

In our series of cases of carcinoma of the pancreas in which the initial involvement is in the tail of the pancreas we find no elevation in the serum lipase values We believe that an elevated serum lipase value will not occur in such instances until the tumor begins to involve the region of the main pancreatic duct which, if it occurs at all, may come on at a time when the functioning pancreatic tissue already has been replaced by tumor tissue, in which case we will anticipate no rise in the serum lipase values

In summary, serum amylase and lipase determinations are simple laboratory procedures of great aid in the diagnosis and treatment of a variety of pancreatic conditions

SERUM PANCREATIC ENZYME VALUES IN ABDOMINAL LESIONS NOT ORIGINATING IN THE PANCREAS

EDWARD C RAFFENSPERGER, M D

Our interest in the elevation of pancreatic serum enzymes in instances other than those associated with primary intrinsic pancreatic disease was aroused by a case in which an elevated serum amylase and lipase level led us to an erroneous diagnosis This mistaken diagnosis probably caused the death of the patient

The patient in question was a fifty year old colored woman who was admitted with a history commensurate with partial intestinal obstruction, but with equivocal physical findings The roentgen diagnosis was partial small bowel obstruction serum amylase determination on the third day of her illness showed 343 mg and the serum lipase was 1 0 cc On the fourth day of the illness the serum amylase was 243 mg and the serum lipase had risen to 2 5 cc

After these determinations we considered acute pancreatitis as the diagnosis of choice with an associated moderate degree of ileus The patient was placed on a strict pancreatic therapeutic regimen On the fifth day of her hospitalization the patient showed the abdominal signs of generalized peritonitis without an elevation of temperature or in the white blood cell count

The patient was operated upon on the seventh hospital day, at which time soupy pus was found throughout the abdominal cavity, and the ileum approximately 15 cm from the ileocecal valve was found to be incarcerated and strangulated beneath a band of adhesions There was a free perforation in this

portion of the bowel The patient died some six hours postoperatively No autopsy was performed and the pancreas could not be inspected at operation

About three weeks later another patient presented himself at the Receiving Ward and gave a history and showed the physical findings of an acute perforated peptic ulcer A roentgenogram for free air under the diaphragm showed no free air A stat amylase determination was 326 mg Because of the classical history and the physical signs, the patient was operated upon and an anterior prepyloric perforated gastric ulcer was discovered and repaired The pancreas at operation was described grossly as being soft. The serum amylase was normal on the day following the operation, but the serum lipase reached a peak of 1 8 cc on the fourth hospital day

The diagnostic and prognostic implications of the serum pancreatic enzyme studies in this case pointed to acute pancreatitis as a definite differential diagnostic possibility However, the clinical signs were so classical that the diagnosis of ruptured peptic ulcer was made If they had not been so clear-cut, we might easily have made the diagnosis of acute pancreatitis and instituted medical therapy instead of recommending the necessary operation

SERUM PANCREATIC ENZYMES IN PERFORATED ULCER

Our interest being aroused, we were then able to collect, over the next year, 21 cases with elevated serum pancreatic enzyme values without primary intrinsic pancreatic disease Five of the 21 cases in this series showed elevated serum pancreatic enzymes in association with perforated peptic ulcers, 4 were acute perforations and 1 a subacute perforation, 3 of the 5 cases had free anterior gastric ulcer perforations, 1 had a subacute pyloro duodenal perforation into the liver, and 1 was an acute posterior lateral perforation of the duodenal cap The highest amylase determination in this group was 326 mg and the highest lipase was 6 2 cc Three of these 5 patients died, 1 who died within thirty-six hours after admission and operation had only one blood examination performed which showed a serum amylase of 209 mg and a serum lipase of 2 3 cc One patient died after ten days during which time he was continuously in delirium tremens and had disrupted his wound, 1 died of pulmonary embolism on the twenty second hospital day Autopsies were performed on 2 of these patients Sections from the pancreas were normal in both cases

SERUM PANCREATIC ENZYMES IN INTESTINAL OBSTRUCTION

Four of our 21 patients had partial intestinal obstruction I have discussed one case The picture in this instance is not clear-cut since generalized acute peritonitis was associated with the obstruction The other 3 cases, however, were instances of simple partial small bowel obstruction, 2 of which responded to Miller Abbott intubation, while the other had an exploratory laparotomy, at which time an internal hernia of the jejunum was reduced and repaired The pancreas was not inspected, unfortunately, at this operation The highest amylase recorded in these 3 cases was 210 mg while the

highest lipase was 2 5 cc The height of the serum amylase and lipase curve in these 3 cases was obtained between the fifth and the fourteenth day following the obstruction There was no correlation between the height of the serum pancreatic enzyme levels and the severity of the patient s symptoms Two patients were totally asymptomatic with serum lipase levels of 1 5 and 2 5 cc

SERUM PANCREATIC ENZYMES IN PERITONITIS

Eight of the 21 patients had acute peritonitis, the causes of the peritonitis were 2 instances of stab wound of the abdomen without bowel perforation, 1 hematoperitoneum of unknown etiology, 1 ruptured urinary bladder, 1 ruptured appendix, 1 ulcerative colitis with subacute perforation of the colon, 1 instance of evisceration from a postoperative wound disruption and 1 case of peritonitis of unknown etiology The highest serum amylase recorded in these 8 cases was 405 mg while the highest serum lipase was 5 2 cc The first elevation of serum amylase and lipase values was from five to seven days following the onset of the peritonitis The peak of the curve was reached five to seven days following the first elevation and concentrations of both enzymes remained increased for two to three weeks In only one of these cases was the pancreas carefully inspected during operation and that was the instance of ulcerative colitis with two walled-off perforations of the colon, with a serum amylase level of 259 mg and a serum lipase level of 3 1 cc twenty four hours before operation The perforations were in the cecum and splenic flexure The latter area was adherent to the stomach but not to the pancreas At operation the pancreas was grossly normal No biopsy was taken In this group of cases we were again unable to correlate the height of the serum pancreatic enzymes with the severity of the symptoms or the prognosis

One of the patients in this series was a thirteen-month infant who was admitted because of hematemesis The child died less than twenty-four hours after admission The only serum amylase determination was 388 mg and the serum lipase was 1 9 cc The autopsy revealed a diaphragmatic hernia with torsion and strangulation of the stomach The pancreas was grossly and microscopically normal

RENAL IMPAIRMENT

The remaining 3 of our 21 patients had elevations of serum enzymes in association with renal impairment One of these patients had been subjected to peritoneal lavage for five days before the serum amylase and lipase values were determined The serum amylase level was 78 mg which was within normal but the serum lipase was 2 8 cc The blood urea nitrogen at this time was 270 mg The generalized subacute peritonitis usually associated with peritoneal lavage possibly influenced the elevated serum lipase value in this case One patient presented a marked uremia with a blood urea nitrogen of 210 mg while at the same time the serum amylase level was

326 mg and the serum lipase was 5 9 cc As this patient improved, the blood urea nitrogen gradually fell This fall was paralleled exactly by the serum pancreatic enzyme levels On the eighteenth hospital day the blood urea nitrogen was 15 mg, the serum amylase value 170 mg and the erum lipase 1 7 cc The last of these 3 patients was an instance of a severe transfusion reaction with renal shutdown The blood urea nitrogen rose rapidly and on the seventh day following reaction was 162 mg, and on the ninth day was 144 mg The serum amylase levels of these two days were within normal limits, but the serum lipase values were 2 2 and 3 0 cc respectively

CONCLUSIONS

In this series only 1 patient had a serum amylase determination of over 400 mg, and this was on the twelfth day of peritonitis following a ruptured appendix Six of the 21 patients had elevations of serum amylase activity above 300 mg, the majority of amylase determinations fell between 200 and 300 mg The highest serum lipase value reported in this series was 6 2 cc. This was obtained in the case of the pyloro-duodenal ulcer with a subacute perforation into the liver Six of the 21 patients had serum lipase values above 4 cc while the majority of the values were between 1 5 and 4 cc Special attention was paid to the time of elevation of the serum pancreatic enzymes in relation to the day of the disease Of the 4 instances of acute perforated peptic ulcer, 2 had elevated serum amylase and lipase values within the first twenty four hours following the perforation while 2 had elevated studies only after eight to ten days In the remaining case the exact time of perforation could not be determined Three of the 4 patients had free anterior perforations of the stomach, the fourth acute perforation was a posterolateral perforation of the duodenal cap An additional case of subacute perforation of the pyloro duodenal ulcer has been cited

When one speculates concerning the cause of the elevated serum pancreatic enzymes in these 5 cases the most attractive hypothesis is that the soiling has produced an inflammation at the posterior peritoneum overlying the pancreas, with possibly some block to the outflow of the external pancreatic enzymes This is pure speculation and on the two sections taken at autopsy no abnormality of the pancreas could be proved The operative trauma probably did not play any part in producing hyperenzymemia

It is of particular interest that in none of these cases did the serum amylase values reach a height such as that which is frequently seen in acute pancreatitis, i e, 500 mg or above It might be reasonable to say that the abdominal pain associated with a serum amylase value of under 500 mg is commensurate with a diagnosis of acute perforation of a peptic ulcer, while an elevation of above 500 mg should make the diagnosis of acute pancreatitis more likely

It would seem from this series that the same generalization cannot be made concerning the serum lipase values Certainly a 6 2 cc reading is as high as many serum lipase values encountered in acute pancreatitis The most important lesson to be learned from these cases is that an elevation

of serum pancreatic enzymes can occur in association with an acute perforated peptic ulcer regardless of the site of the perforation

In the 4 cases of partial small bowel obstruction with elevated serum pancreatic enzymes, the height of the determinations was first seen six to eight days following the obstruction The serum lipase values showed a higher comparative elevation than did the serum amylase values The average peak elevation of the serum amylase values was 180 mg while the average peak lipase value was 2 1 cc There is no proved explanation for this elevation of serum pancreatic enzyme values that I could find but it is important to know that such elevations can occur in association with partial small bowel obstruction since it is of differential diagnostic importance in distinguishing between actual mechanical obstruction and the ileus which may be associated with acute pancreatitis

Acute peritonitis of almost any etiology may give elevated serum pancreatic enzyme values These elevations were first seen from five to ten days following the insult and were equally reflected in both of the serum pancreatic enzyme values The values remained elevated for a longer time in this group than any of the others The elevations of the serum pancreatic enzymes in association with acute peritonitis do not have the differential diagnostic importance of the preceding two groups Evidently there is a degree of pancreatic insult associated with the occurrence of acute peritonitis and this insult is reflected in the elevated serum pancreatic enzyme values for comparatively long periods of time, even after the patient has become totally asymptomatic Just how important this pancreatic insult is to the prognostic evaluation of the case, it is difficult to say

Three patients with uremia showed elevations of the serum pancreatic enzyme values in association with the elevation of the blood urea nitrogen In the patient with acute exacerbation of chronic glomerular nephritis, there was a complete parallelism of these three laboratory tests, as the patient recovered all three fell in a straight curve It would seem that the elevations of the serum pancreatic enzymes in this case were on an impaired excretory basis

Finally, in none of these 21 cases was it possible for us to correlate the severity or the prognosis of the disease with the time degree or duration of elevation of the serum pancreatic enzyme values

326 mg and the serum lipase was 5 9 cc As this patient improved, the blood urea nitrogen gradually fell This fall was paralleled exactly by the serum pancreatic enzyme levels On the eighteenth hospital day the blood urea nitrogen was 15 mg, the serum amylase value 170 mg and the serum lipase 1 7 cc The last of these 3 patients was an instance of a severe transfusion reaction with renal shutdown The blood urea nitrogen rose rapidly and on the seventh day following reaction was 162 mg, and on the ninth day was 144 mg The serum amylase levels of these two days were within normal limits, but the serum lipase values were 2 2 and 3 0 cc respectively

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It would seem from this series that the same generalization cannot be made concerning the serum lipase values Certainly a 6 2 cc reading is as high as many serum lipase values encountered in acute pancreatitis The most important lesson to be learned from these cases is that an elevation

The fasting residuum of the stomach was aspirated before the gastroduodenal tube was permitted to progress into the duodenum Under fluoroscopic guidance, the progress of the Miller-Abbott tube was observed, and when the tip reached the duodenal cap the balloon was inflated whereupon peristalsis immediately conveyed the tube through the duodenal loop to the ligament of Treitz Continuous aspiration of the gastric and duodenal contents was carried out for thirty minutes or longer before the administration of one of the stimulants

In the studies with secretin, a standard dosage of 80 units of the Wyeth product was given intravenously, and the continuous aspiration was maintained thereafter for one hour The samples were fractionated at the end of ten twenty, forty and sixty minutes

Pancreatic stimulation by means of secretin is characterized by a large volume of secretion possessing a high concentration of bicarbonate The concentration of enzymes in pancreatic juice seems to be under the influence of vagal stimulation

RATE OF SECRETION

Aspiration of the duodenal contents during the fasting period yielded some material in practically all of the cases studied It is estimated that this fluid is secreted at a rate of 0 5 to 1 cc per minute The variability in the amounts obtained, it is believed resulted from the degree of activity of the pancreas at the time whereas the pathologic involvement of the pancreas was thought to be a minor factor

In three studies the amount of duodenal contents obtained prior to the injection of secretin was less than 10 cc regardless of the duration of this period Of the three individuals in whom this occurred, one has had pancreatic achylia for many years a second had had a complete supradiaphragmatic vagotomy, and the third had a large pancreatic cyst In general there was little or no difference between the volume of fasting secretion in the normal material and that in the pathologic material

Immediately following the administration of secretin the rate of secretion as measured by noting the volume of the duodenal contents rose very rapidly In a group of normal individuals the mean rate of secretion in the first ten minutes was 3 8 cc This tended to drop slightly during the next ten-minute interval to a figure of 3 0 cc and in the last twenty minutes of the hour the pancreas was still secreting at the rate of 1 9 cc per minute The range of the rate of secretion was rather variable The lowest rate of secretion observed was just slightly in excess of 1 cc per minute and the highest rate found during the first ten minutes was 8 0 cc *

In a group of individuals with relapsing pancreatitis who at the time of the intubation study had elevation of the serum enzymes, either one or both, the mean rate of secretion was not too different as a matter of fact it

* I use pancreatic secretion and duodenal contents rather interchangeably although I realize these terms are not synonymous

EXPERIENCE WITH SECRETIN AND OTHER PANCREATIC STIMULANTS IN THE STUDY OF PANCREATIC FUNCTION

MIECZYSLAW S LOPUSNIAK, M D

The physiologist is able to measure directly the flow of pancreatic juice by cannulating the pancreatic duct Dr Thomas showed you a diagrammatic sketch of such a procedure this morning In the clinical appraisal of pancreatic function in humans we are able to examine the duodenal contents, but this fluid is a mixture of the secretions from the pancreas, the stomach, the biliary tree and the duodenal mucosa It is possible to eliminate one of these secretions, that from the stomach, by means of a gastroduodenal tube

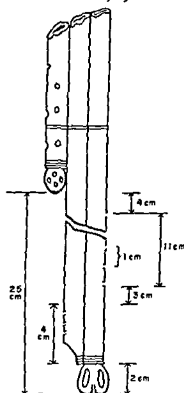


Fig 160 Diagram of gastroduodenal tube

The particular gastroduodenal tube used in these studies was made by combining a Rehfuss tube with a Miller-Abbott tube The diagram in Fig 160 shows the relative position of the distal portions of these two tubes One lumen of the Miller-Abbott tube was used to inflate a balloon that facilitated the intubation of the duodenal loop through the other lumen, duodenal secretions were removed

with a mean value of 152 cc In those patients in whom it was suspected that the pancreas had a certain degree of fibrosis the volume was roughly two-thirds of the mean volume The range in the latter group varied from 4 cc in one individual who had pancreatic achylia and a labile diabetes mellitus to 322 cc In the group with relapsing pancreatitis the mean hourly volume was slightly less than that found in the normal material The following table shows these values

Table 23 Volume of Secretion

	IN NORMAL PATIENTS	IN PATIENTS WITH RELAPSING PANCREATITIS	IN PATIENTS HAVING CHRONICALLY DISEASED PANCREAS
	cc	cc	cc
Maximum	301	337	322
Mean	152	137	102
Minimum	75	34	4

The maximum pancreatic flow occurred during the first twenty minutes after hormonal stimulation in almost all of the pancreatic function studies Forty five per cent of the sixty minute volume in the normal material was collected in those first twenty minutes in the relapsing pancreatitis group, 47 per cent and in the third group, 41 per cent Since the rate of pancreatic flow in the pathologic group is practically identical to the rate of flow in the normal group it is tempting to suggest that the total volume of secretion may be a measure of the mass of functioning pancreatic cells

BICARBONATE

During the fasting period the bicarbonate concentration either determined by the Van Slyke apparatus or calculated by determining the neutralizing capacity of the duodenal contents is rather low These values do not give any information about the ability of the pancreas to secrete bicarbonate following hormonal stimulation After the injection of secretin the concentration of bicarbonate increased rapidly, but not to the same degree as the rate of secretion however, the outpouring of bicarbonate continued even though the secretory rate fell toward the end of the hour

In our normal patients, at some time during the sixty minutes after the administration of secretin, the bicarbonate concentration rose to a value of 85 to 115 milliequivalents per liter this corresponds to a range of 200 to 260 volumes per cent of carbon dioxide as determined by the Van Slyke apparatus The acid combining power of the duodenal contents exhibited values 10 to 20 milliequivalents higher than those determined by the Van Slyke method In the individuals with relapsing pancreatitis most of the duodenal specimens showed values for the bicarbonate concentration that are within the range of

was almost identical to that found in the group of normal individuals The range was likewise almost that found in the normal group (Table 21)

Table 20 Rate of Secretion in Normal Material

	MINUTES FOLLOWING SECRETIN STIMULATION			
	10	20	40	60
Maximum	8 0	5 9	5 1	3 8
Mean	3 8	3 0	2 4	1 9
Minimum	1 0	1 4	1 2	0 9

Table 21 Rate of Secretion in Relapsing Pancreatitis

	MINUTES FOLLOWING SECRETIN STIMULATION			
	10	20	40	60
Maximum	8 5	6 5	5 0	4 4
Mean	3 2	3 1	2 9	1 7
Minimum	1 2	1 0	1 0	0 1

Table 22 Rate of Secretion in Chronic Material

	MINUTES FOLLOWING SECRETIN STIMULATION			
	10	20	40	60
Maximum	5 7	8 2	6 0	4 0
Mean	2 7	2 4	1 5	1 1
Minimum	0 0	0 0	0 03	0.2

In another group with chronic pancreatitis and repeated attacks of inflammation over a number of years, the mean rate of secretion was roughly two thirds of that found in the normal group of individuals (Table 22)

VOLUME

The volume of secretion for a period of sixty minutes after the administration of 80 units of secretin in the normal group ranged from 75 to 301 cc

values for duodenal amylase were practically identical with those found in the normal group

PANCREATIC LIPASE

While in some of the studies there seemed to be a gradual increase in lipolytic activity following hormonal stimulation in general the lipolytic activity of the duodenal contents was unaffected by secretin stimulation In the normal individual the lipase concentration of 1 cc of duodenal juice during the fasting period is equivalent to 15 cc of tenth normal sodium hydroxide This value was generally found in the patients with relapsing pancreatitis

After the administration of secretin the concentration of pancreatic lipase was elevated to a value of 20 to 25 cc of N/10 NaOH and this was maintained almost uniformly for a period of sixty minutes Some of the individuals with relapsing pancreatitis showed elevations in the lipolytic activity of the duodenal contents after secretin but this concentration decreased toward the end of the hour I have the feeling that this group of individuals exhibited a certain degree of steatorrhea when the fat content of the feces was deter mined chemically

NITROGEN

The nitrogen content of the duodenal contents was determined in some of the cases by means of the Kjeldahl method Though the curves are not exactly parallel, there is some correlation between the concentration of amylase and the nitrogen there is no relation between the nitrogen and the lipolytic activity however It is realized that, at best, the nitrogen content is a crude measure since we are not dealing with pure pancreatic secretion

CHOLERETIC ACTION

Secretin, in addition to stimulating the flow of pancreatic juice, has a certain choleretic action If one measures the bile concentration in the duodenal samples after hormonal or secretin stimulation there are four patterns The individual who had had a cholecystectomy and the patient who had a nonfunctioning gallbladder tended to pour out a fairly high concentration of bile in all the specimens In a normal patient who had a normally functioning gallbladder at the time of intubation, at some time during the one-hour period after the administration of secretin, the bile tended to disappear from the duodenal contents and flowed into the gallbladder In the fourth type there was a total absence of bile in all duodenal contents resulting from a complete obstruction in the common duct In our series we had one such case in which it was predicted the surgeon would find a pathologic obstruction proximal to the ampulla of Vater This patient had a papillary adenocarcinoma of the common duct within the substance of the pancreas

INSULIN HYPOGLYCEMIA

The response of the pancreas during a state of hypoglycemia was studied in 4 patients with duodenal ulcer, one of whom had had a complete supra-

normal, whereas in those whose pancreases have been involved by repeated attacks, the values were considerably lower

Table 24 Acid Combining Power in Milliequivalents/Liter

	MINUTES FOLLOWING SECRETIN STIMULATION				
	FASTING	10	20	40	60
Normal Material					
Maximum	40	132	127	126	118
Mean	24	75	108	101	84
Minimum	12	33	85	41	28
Relapsing Pancreatitis					
Maximum	27	84	112	118	112
Mean	18	47	83	81	70
Minimum	7	12	48	32	33
*Chronically Diseased Pancreas**					
Maximum	35	73	101	111	81
Mean	23	37	67	60	50
Minimum	15	17	39	41	13

* It is rather interesting to note that in the last group the volume and the bicarbonate concentration are both depressed, which may be some measure of the acinar mass or functioning pancreatic tissue

AMYLOPSIN

During the fasting period the enzyme concentrations may give us a little more information if we measure the pancreatic amylase in a manner similar to the method used for the blood In the normal individual we found that the amylolytic power of 1 cc of duodenal juice was equivalent to a sugar solution whose concentration is 2 to 3 2 per cent—that is, 2 to 3 2 gm of glucose in 100 cc of water In patients with relapsing pancreatitis the amylolytic power of the fasting duodenal juice was considerably less, the range was from 0 8 to 2 3 In other words, it was at the lowermost level for the normals

The data on the amylolytic concentrations of the duodenal contents show that secretin stimulation may be followed by a slight increase in the starch splitting activity, a second rise in the concentration occurs toward the end of the hour Between these two peaks, the duodenal contents usually exhibit a diminution in amylolytic activity This particular pattern has been observed not only in normal material, but also in the pathologic group

A diminution in the concentration of amylopsin may be found if the intubation procedure is performed before recovery has occurred in a case of acute pancreatitis In one patient, approximately three weeks after a mild attack of relapsing pancreatitis, the amylolytic activity of the duodenal contents in response to secretin was increased from 0 8 to 1 9 per cent of glucose In the same patient, four weeks after another attack, the enzyme

2 Parasympathetic or urecholine action which is characterized by an increase in enzyme concentration

The role of the blood sugar in the metabolism of the acinar cell probably is very important

We think that secretin has been helpful in the detection of mild disturbances of pancreatic function

RECENT EXPERIENCE IN THE DIAGNOSIS AND TREATMENT OF ACUTE PANCREATITIS

HENRY L BOCKUS, M D

I do not propose to cover all of the clinical aspects of acute pancreatitis I merely wish to stress some features of the disease that have interested us as a result of the recent labor of Dr Raffensperger, who was kind enough to review carefully 10 consecutive patients with acute inflammation of the pancreas seen at the Graduate Hospital over a period of fourteen months *

DEFINITION

By way of introduction I should like to mention the change which has occurred in our concept concerning the definition of acute pancreatitis Previously, as a result of that very good paper of Fitz back in 1889,[13] the term acute pancreatitis was applied only to those cases associated with marked necrosis and hemorrhage Recently it has become well recognized that insult to the pancreas causing acute inflammation is not always associated with recognizable necrosis either in the pancreas or surrounding tissues or with recognizable hemorrhage into the tissues As a result of observations at necropsy and operation, together with the experience of many observers with pancreatic serum enzyme determinations many instances of less severe acute inflammation of the pancreas with little or no necrosis have been recognized and described This milder type of inflammation is usually termed edema of the pancreas Acute edema of the pancreas has been recognized most often in association with acute episodes of biliary tract disease In fact, it has become customary to consider acute edema of the pancreas as being commonly due to acute episodes of biliary tract disease It should be borne in mind, however that any mechanism which is capable of causing acute necrosis may at times cause only edema of the pancreas without concomitant necrosis

Perhaps the only tenable concept concerning the pathogenesis of acute pancreatitis is that all grades of acute inflammation of the pancreas, with or without massive necrosis are but manifestations of the same basic process,

* Our experience with these cases has been reported previously (New York State Medical Journal Vol 48 No 20 Oct 15 1948)

diaphragmatic vagotomy Vagal impulses, arising from central stimulation, can be produced by 15 units of regular insulin given intravenously, however, sympathetic stimulation also occurs as a result of the hypoglycemia

With continuous aspiration for a period of two hours, 20, 31 and 53 cc of duodenal contents were removed in three of the cases, 13 cc in the vagotomized patient The increase in the icterus index following the injection of insulin suggested that the gallbladder had contracted, this response was not noted in the patient with severed vagi The bicarbonate concentration of the duodenal contents was practically unaffected by insulin

The lipolytic activity of the duodenal contents paralleled the course of the blood sugar

Experimentally, Babkin and his group found that the concentration of enzymes in pancreatic fluid was considerably depressed when the blood sugar was low even though the volume was not decreased in every case by the hypoglycemia This effect was found only when the vagi were intact When they administered glucose intravenously to these animals, they noted that the concentration of the enzymes increased, and in those cases in which the volume of secretion was low, the volume was elevated to its normal value These authors thought that the intravenous glucose probably acted directly upon the pancreatic cells, and that this was an example of peripheral parasympathetic action

URECHOLINE

Two individuals who had had secretin studies, earlier, were given urecholine In the patient with pancreatic achylia, 4 and 11 cc of duodenal contents were aspirated hourly after successive doses of 80 units of secretin After the administration of 10 mg of urecholine subcutaneously, a volume in excess of 100 cc per hour was obtained the icterus index of which was very high The concentration of bicarbonate was very, very low after urecholine, following secretin stimulation it was slightly higher, but still depressed The enzyme values after secretin were almost absent, urecholine did produce a marked increase, but this was only a temporary effect, and the enzyme activity of the duodenal contents disappeared during the latter part of the hour

In a second individual whose pancreas has been involved by fibrosis, 90 cc of duodenal contents was aspirated after secretin, 52 cc following urecholine The bicarbonate concentration was higher after secretin than after urecholine, while the increase in the icterus index was greater after urecholine The concentration of pancreatic enzymes was increased by urecholine, but remained depressed following secretin

SUMMARY

In the evaluation of pancreatic function two types of stimulation can be used

1 Hormonal or secretin action which can be evaluated by the volume of secretion and the bicarbonate concentration and

2 Parasympathetic or urecholine action which is characterized by an increase in enzyme concentration

The role of the blood sugar in the metabolism of the acinar cell probably is very important

We think that secretin has been helpful in the detection of mild disturbances of pancreatic function

RECENT EXPERIENCE IN THE DIAGNOSIS AND TREATMENT OF ACUTE PANCREATITIS

HENRY L BOCKUS, M D

I do not propose to cover all of the clinical aspects of acute pancreatitis I merely wish to stress some features of the disease that have interested us as a result of the recent labor of Dr Raffensperger, who was kind enough to review carefully 10 consecutive patients with acute inflammation of the pancreas seen at the Graduate Hospital over a period of fourteen months *

DEFINITION

By way of introduction, I should like to mention the change which has occurred in our concept concerning the definition of acute pancreatitis Previously, as a result of that very good paper of Fitz back in 1889,[1 3] the term acute pancreatitis was applied only to those cases associated with marked necrosis and hemorrhage Recently it has become well recognized that insult to the pancreas causing acute inflammation is not always associated with recognizable necrosis either in the pancreas or surrounding tissues, or with recognizable hemorrhage into the tissues As a result of observations at necropsy and operation, together with the experience of many observers with pancreatic serum enzyme determinations many instances of less severe acute inflammation of the pancreas with little or no necrosis have been recognized and described This milder type of inflammation is usually termed edema of the pancreas Acute edema of the pancreas has been recognized most often in association with acute episodes of biliary tract disease In fact it has become customary to consider acute edema of the pancreas as being commonly due to acute episodes of biliary tract disease It should be borne in mind, however that any mechanism which is capable of causing acute necrosis may at times cause only edema of the pancreas without concomitant necrosis

Perhaps the only tenable concept concerning the pathogenesis of acute pancreatitis is that all grades of acute inflammation of the pancreas, with or without massive necrosis are but manifestations of the same basic process,

* Our experience with these cases has been reported previously (New York State Medical Journal Vol 48, No 20 Oct 15 1948)

merely representing varying degrees of inflammatory response to the insulting agent Various factors undoubtedly enter into the degree of response which occurs They must include the following (1) the presence or absence of antecedent pancreatic inflammation, (2) the modus operandi of the inciting cause or causes, (3) the presence or absence of obstruction to the outflow of pancreatic juice, (4) the degree of escape of pancreatic enzymes into the surrounding tissues, and (5) the presence or absence of a disturbance of the blood supply to the pancreas In the early stages of an attack it is not possible to prognosticate with certainty whether the inflammation will be characterized by edema alone with little or no necrosis or whether extensive necrosis will take place

ETIOLOGY

In these recent cases of ours (10 in all), the review of the etiology is rather interesting in that 4 of these patients were, to some extent, alcoholic (40 per cent) and in 3 of them *the acute attacks were related to imbibing* excessive amounts of alcohol In one of them there was a combination of biliary tract disease and alcoholism In 5 patients (50 per cent) there was evidence of biliary tract disease *It may be seen that in the study of 10* consecutive patients with acute pancreatitis, 9 of them either gave histories of imbibing excessive amounts of alcohol or showed evidence of biliary tract disease These two etiologic factors are unquestionably the more important ones, they constitute the essential etiologic agents which can be held responsible for the initiation of acute catastrophic attacks of pancreatitis

DIAGNOSIS

Now a word concerning the clinical features of acute pancreatitis I believe that it is impossible by bedside examination alone to make an unequivocal, definitive diagnosis of acute pancreatitis The possibility of this diagnosis usually is considered, but, by history and physical findings alone, to differentiate all of the conditions which acute pancreatic necrosis simulates, is something that I have not been able to do

Time does not permit of a detailed discussion of many of the clinical masquerades of acute pancreatitis I should like to mention that often it simulates an acute abdominal emergency like that produced by a ruptured viscus, that the presence of a shock-like state in any patient with severe abdominal pain should cause acute pancreatitis to be considered, that the presence of *unusual vascular skin markings in any patient* with acute abdominal pain should cause one to think of the possibility of acute pancreatitis since it is the most common acute abdominal inflammation giving rise to queer cyanotic markings blotchy brownish or bluish discolorations on the back, the abdomen, the buttocks and the legs It is more likely to be associated with acute thrombophlebitis, perhaps, than any other acute abdominal condition

We have had difficulty in making the differential diagnosis between acute pancreatitis and coronary thrombosis as well as basal pneumonitis and/or

pleurisy The presence of abdominal signs at the left base has been mentioned in association with acute pancreatitis for many years I was interested to hear A H Aaron in a recent discussion of this topic say that at the Buffalo General Hospital it was not unusual to recover fluid from the left pleural sac in patients with acute pancreatitis Other conditions which caused difficulty in differential diagnosis in our experience include acute alcoholic gastritis, acute appendicitis acute diverticulitis and bowel obstruction It is important to make the differential diagnosis early since it is our belief that usually acute pancreatitis should be treated medically whereas many conditions which it simulates clinically require early surgical intervention

SERUM ENZYME TESTS

Fortunately certain laboratory determinations have pathognomonic value in the early diagnosis of acute pancreatitis I refer to the concentrations of serum amylase and lipase Drs Johnson and Raffensperger have discussed the clinical application of these tests You will recall that Dr Raffensperger has obtained elevations in the serum enzyme values in acute abdominal conditions other than acute pancreatitis e g , in intestinal obstruction and in peritonitis However, in the relatively large series of patients studied by Dr Raffensperger there was not a single instance of a rise in the serum amylase above 500 mg in abdominal conditions other than primary disease of the pancreas We feel therefore, that increases in the concentration of serum amylase above 500 mg in patients with acute abdominal symptoms are indicative of acute pancreatitis In practice, then in patients with acute abdominal symptoms, if the serum amylase value (which is available within one hour) is above 500 mg the patient is treated medically in the beginning (in the absence of clear cut signs of peritonitis or ruptured viscus)

On our service it has become routine to order serum enzyme determinations at once under the following circumstances (1) presence of symptoms and signs suggestive of acute biliary tract disease (2) patients with acute abdominal pain of undetermined origin particularly in subjects addicted to alcohol, (3) presence of upper abdominal or back pain in association with a shock like state and (4) instances of trauma or injury of the abdomen One must remain pancreas conscious and remember to order the essential serum enzyme tests in order to arrive at the correct diagnosis early and avoid delay in the institution of essential therapeutic measures The relative merit of determinations of serum amylase and of serum lipase has been discussed by Dr Johnson and requires no reiteration

BLOOD CALCIUM VALUES

In the study of our patients with acute pancreatitis we have become interested in the blood calcium levels because of the contribution of Edmond son and Berne[4] We were quite surprised when we first read their paper to learn of the tremendous amount of calcium which may be mobilized in and around the pancreas in acute pancreatic necrosis Sufficient calcium can be withdrawn from the blood stream to cause an actual lowering in the blood

calcium values Edmondson and Berne reported blood calcium values below 9 mg in 70 per cent of their cases of proved acute necrosis of the pancreas In their group of cases, if the serum calcium level was lower than 7 mg, the prognosis proved hopeless Four of our 10 patients had hypocalcemia occurring somewhere between the second and the sixteenth day (Fig 161) This slide records our experience with the serum calcium values in 4 of our cases having hypocalcemia (A composite curve of the serum amylase and lipase values is also drawn) In our cases the lowest calcium values were obtained on the fourteenth day

In the group of cases reported by Edmondson and Berne the lowest calcium determinations occurred in about seven days Calcium determinations have no value in the diagnosis of acute pancreatitis at the time of the emergency, but the calcium value probably can be correlated to some extent

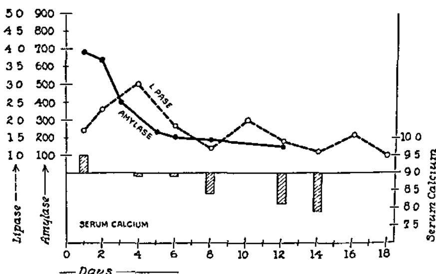


Fig 161 Composite curve of average mean blood calcium values in 4 cases of acute pancreatitis The composite curves of concentrations of serum amylase and lipase during the course of acute pancreatitis in 8 patients are also shown

with the degree of necrosis which has occurred in or around the pancreas, since the drop in serum calcium is evidently due to the withdrawal of calcium from the blood to combine with the fatty acids which have been formed by the destruction of fat in and around the pancreas

ELECTROCARDIOGRAPHIC CHANGES

Not infrequently, in the differential diagnosis of acute pancreatitis, coronary occlusion must be excluded One must also consider the concomitant occurrence of cardiac insult because of the associated shock and at times of a marked disturbance in electrolyte balance due to vomiting, dehydration, etc Obviously, these changes would be most marked in patients with antecedent cardiovascular disease In 5 patients with acute pancreatitis, Gottesman and his associates have reported the occurrence of electrocardio

graphic changes simulating those of coronary thrombosis[5-6] The abnormalities in the tracings were present when the patients were acutely ill and when the serum amylase was elevated With improvement in the clinical status of the patient and a return of the serum amylase concentration to normal, the electrocardiographic changes disappeared In their patients there was depression of the S–T segment in leads 2 and 3 and diphasic T waves were noted in leads 1, 2 and 3 Six days later the T wave in lead 1 was inverted, and the T wave of lead 2 was diphasic, whereas fourteen days after the onset of the acute pancreatitis the tracings were normal

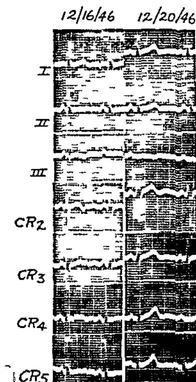


Fig 162 This patient (C B) three days after admission with acute pancreatitis (December 16) showed evidence of myocardial abnormality Four days later the tracing was essentially normal

In 3 of our patients with acute pancreatitis, electrocardiographic changes were noted In this slide (Fig 162) four days after admission the heart rate was 84 and P-R interval 0 14 second The rhythm, P waves and QRS complexes were normal The RS-T segments were isoelectric the T waves were low in amplitude in L_2, CR_3 CR_4 and CR_5 and were inverted in CR_2 This tracing was interpreted by our cardiologist Dr Samuel Bellet, as showing evidence of myocardial abnormality The electrocardiographic tracing, recorded four days after the first tracing was considered to be normal

Twenty two serial electrocardiographic tracings were performed on H F during the course of eight weeks observation (Fig 163) In general, the interpretation of the tracings was that of acute lateral myocardial infarction The abnormal findings improved but did not completely disappear during this period It should be noted that the patient was extremely ill, being comatose for one week Diabetes mellitus occurred during the course of the illness
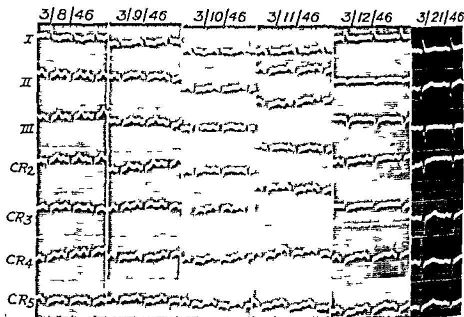


Fig 163 Serial tracings in a patient with acute severe pancreatic necrosis At the time of the first tracing the patient was in shock with a serum amylase value of 989 mg Acute lateral coronary infarction was suspected The abnormal findings improved but did not entirely disappear

As a result of the study of the electrocardiographic tracings in these three and in several other patients observed by Dr Bellet, he has expressed the following opinion

'Profound changes occur in the electrocardiographic tracings in many patients with acute pancreatitis They include inversion of the T waves in lead I, in the other limb leads, and in the precordial leads, accompanied by varying degrees of depression of the S-T segment These changes gradually return to normal with improvement in the clinical state of the patient These findings in conjunction with the clinical picture might be confused with the findings of acute myocardial infarction

He expressed the opinion that the electrocardiographic changes in acute pancreatitis are to some extent the result of the shock like state, particularly in older individuals with coronary arteriosclerosis He likewise has considered the possible effect of a diminution in the concentration of serum potassium He believes that decreased serum potassium values could occur in association

with acute pancreatitis, particularly if vomiting or dehydration has accompanied the illness and if the patient is treated with large amounts of parenteral fluid and/or Wangensteen drainage He also mentioned that the loss of serum potassium may be increased in patients with concomitant diabetes mellitus, since the administration of insulin and glucose may still further diminish the concentration of serum potassium

I am of the opinion that the causes of the electrocardiographic changes occurring in association with acute pancreatitis have not been clearly established but certainly the factors mentioned by Bellet should be given serious consideration I have presented the electrocardiographic examinations of these patients in some detail in order to emphasize the possibility of arriving at an erroneous diagnosis of acute coronary occlusion in patients with acute pancreatitis This mistake is not likely to occur if serum enzyme determinations are performed Unfortunately, coronary occlusion may occur in association with pancreatic necrosis rendering the complete diagnosis very difficult

TREATMENT

I should like to use the few minutes remaining to discuss the most practical phase of this problem namely its treatment Formerly immediate operation was frequently employed in the treatment of acute pancreatic necrosis The mortality following immediate operation is something more than 50 per cent [7, 9] In 1927 Schmieden and Sebening culled from the literature a total of 1278 cases of acute pancreatitis treated by operation, resulting in a mortality of 51 2 per cent DeTakats and MacKenzie[10] were apparently the first observers to question seriously the concept that acute pancreatitis was a surgical emergency They observed that only 8 of 22 patients with acute pancreatitis who were not operated on within the first twenty four hours died (a mortality of 36 6 per cent) In 1934 Mikkelson[11] reported 39 instances of acute pancreatitis, 20 of those patients were acutely ill and were treated conservatively in the acute stage of the disease The mortality in this group was only 7 5 per cent It is now generally agreed that immediate operation is unwise, providing other acute abdominal emergencies can be excluded It is thought best to withhold operation during the acute stage of pancreatitis unless it becomes complicated by suppuration, severe hemorrhage or spreading peritonitis After convalescence from the acute attack if a severe complication has not developed definitive biliary tract surgery is required in many patients Obviously because of the peculiar physiologic activity of the pancreas, a plan of medical treatment destined to curtail excessive pancreatic function is required Rowland[1] devised such a plan An outline of the principles of treatment employed in our patients follows

RELIEF OF PAIN

Aside from the unpleasantness of pain it must be looked upon as definitely deleterious to the organism and certainly to the myocardium It has been pointed out by Popper and others that morphine should not be used because of its possible vagotonic action At any rate in our experience it is a frequent

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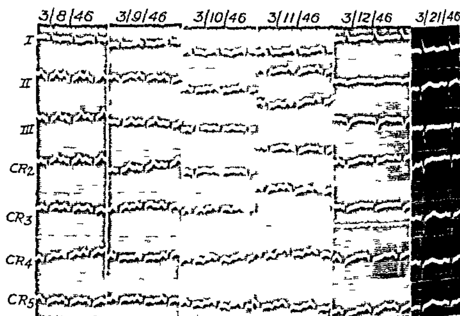


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OTHER MEASURES

Perhaps some thought should be given to the possible occurrence of hypocalcemia in patients who have suffered very acute attacks of pancreatitis Blood calcium determinations should be carried out, at least after the third day, and calcium gluconate administered parenterally if a calcium deficit is detected

The length of time in which the more rigid type of therapy is to be carried out depends upon the clinical status of the patient Recovery from shock, return of the temperature to normal, a drop in the leukocyte count, and recedence of the physical evidences of inflammation constitute the most important guides

Our enthusiasm for the plan of treatment outlined above seems justified in view of recovery in 100 per cent of patients, an experience which was unheard of in the treatment of acute pancreatitis on our service previously It should be stated, however that in only 3 of our patients was a diagnosis of acute severe massive necrosis of the pancreas entertained In 3 of the remainder it was thought that the inflammation was of lesser degree and the lesions were classified as examples of acute edema In the remaining 4 cases proof was finally obtained supporting a primary diagnosis of chronic interstitial pancreatitis, and our treatment was carried out for a severe episode of acute inflammation of the pancreas superimposed upon chronic interstitial pancreatitis

As a last word I should like to reiterate the statement that these patients must be watched carefully day by day to make sure that they are not developing a complication which requires surgical intervention A small percentage of patients will develop a hematoma, an acute cyst, a large suppurating mass or spreading peritonitis and, of course will have to be operated upon

Finally, it should be remembered that after subsidence of the acute attack often these patients do not remain well In my opinion a great majority of patients who have had an attack of acute pancreatitis experience recurrences of either acute or subacute pancreatitis I believe that so-called chronic relapsing pancreatitis is not a rare condition Subsequent attacks may be provoked by marked indiscretions in eating and commonly follow the taking of too much alcohol These patients should be advised never to use alcoholic beverages After subsidence of the acute attack the biliary tract should be studied If they have as a number of them do biliary tract calculus or gallbladder disease operation on the biliary tract is advised

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cause of nausea and vomiting Demerol evidently has an atropine like action and may be looked upon as the analgesic of choice Phenobarbital may likewise be given as needed Paravertebral block on the left side at the level of the eighth to tenth thoracic spinal processes has been used in several patients by Popper with good results We have had no experience with this method in acute pancreatitis but have employed it in the management of intractable pain in chronic relapsing pancreatitis

TREATMENT OF SHOCK AND DEHYDRATION

Every effort should be made to overcome shock as quickly as possible by the administration of plasma and blood transfusions as required Because of the complete fasting which is recommended for these patients, sufficient parenteral fluid is required to maintain normal renal function and good electrolyte balance A word of caution is needed in the administration of glucose and insulin Diabetes mellitus accompanies acute pancreatic necrosis occasionally Glucose infusion must be given cautiously with frequent blood sugar determinations With the occurrence of hyperglycemia sufficient insulin is required with each glucose infusion Usually 5 to 10 units of regular insulin are given subcutaneously with each 25 gm of glucose intravenously Of even greater importance is the necessity for avoiding insulin shock and hypoglycemia The vagotonic action of hypoglycemia on pancreatic secretion may prove deleterious We have usually employed either 2 5 or 5 per cent glucose solutions, slowly infused, and have avoided the use of solutions of greater concentration

MEASURES ADOPTED TO AVOID HORMONAL STIMULATION OF THE PANCREAS

When acute pancreatitis is suspected, a nasal tube should be introduced into the stomach at once and constant Wangensteen suction begun Care must be taken to maintain the position of the tube proximal to the pylorus in order to avoid the passage of gastric juice containing hydrochloric acid into the duodenum We have been in the habit of administering either soluble or insoluble alkalis every one or two hours during the period of Wangensteen suction If these measures are carried out meticulously, it is likely that the hormonal phase of pancreatic secretion may be suppressed

MEASURES TO AVOID NERVOUS STIMULATION OF THE PANCREAS

Atropine sulfate in the dose of 1/75 to 1/150 grain every four hours is employed to depress vagal activity It is hoped that this may likewise tend to reduce the volume of gastric secretion Incidentally, I should like Dr Thomas (our physiologist) to comment later upon the value of atropine in depressing the nervous phase of pancreatic secretion Perhaps ephedrine may similarly assist in the inhibition of flow of pancreatic juice Obviously, drugs which stimulate the vagus nerves, such as prostigmine, which might conceivably be used to overcome distention, are to be withheld

*Table 25 Poll of Impressions of Chief Diagnostic Criterion in Cases of Carcinoma of the Pancreas**

STATUS	NUMBER POLLED	NUMBER OF DIFFERENT SCHOOLS REPRESENTED	DIAGNOSTIC CRITERIA								
			Painless Jaundice	Jaundice	Pain	Loss in Weight	Anorexia	Dyspepsia	Enlarged Gall bladder	Deformed Duodenum	Diabetes
Fourth year medical students	34	4	10	23	—	—	—	—	1	—	—
Interns and residents	36	14	24	10	1	—	—	—	—	1	—
Graduate students	26	23	9	14	1	—	1	1	—	—	—
General practitioners (in practice years or less)	21	6	9	1	1	1	—	—	—	—	1
Total	1 0	34	No 52 43 3	No 59 49 1	No 3 ? 5	No 1 0 8	No 1 0 8	No 1 0 8	No 1 0 8	No 1 0 8	No 1 0 8
			92 5 %		-5%	5 0%					

* From Arch Int Med 68 5?5 1941

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DIAGNOSIS OF CARCINOMA OF THE PANCREAS

J EDWARD BERK, M D

If operations involving partial and even total pancreatectomy are to be gainfully employed in the treatment of patients with pancreatic cancer, early diagnosis is essential Yet, despite the incentive afforded by these potentially curative surgical procedures, the diagnosis of carcinoma of the pancreas is generally not made until the disease is well advanced

PROBLEMS IN DIAGNOSIS

Many reasons may be adduced to help explain this delay in diagnosis Not the least important is the fact that the gland is notoriously difficult to examine Its deep location handicaps ordinary physical examination and there is as yet no way of making it directly visible to x-ray Moreover, none of the presently applied tests of pancreatic function establishes the diagnosis of cancer to the exclusion of all other disorders which may affect this structure Hence, even when the diagnosis is made, it is still essentially presumptive

Another reason contributing to delay in diagnosis is the fact that our concept of the clinical picture of the disease is based largely upon findings in individuals in whom the disease was in its advanced stages This has tended to fix in our minds only the late manifestations

Still another factor tending to retard diagnosis is the persistence of erroneous notions regarding the clinical picture Some nine years ago, we undertook a survey intended to supply some information as to just what the notions were regarding the clinical features of this disorder In the light of the recent presidential election, and aware of the fact that there must be in this room several true and tried Democrats, it is with great reluctance that I show the results of that poll

Four otherwise unselected groups of people were questioned They represented (1) fourth year medical students, (2) interns and residents, (3) graduate medical students and (4) general practitioners who had been in practice for five years or less In all 120 individuals who had graduated or were about to graduate from 34 different medical schools were queried After first explaining the nature and purpose of the poll without mentioning the disease in question, each person was asked what feature he associated

In the light of our present knowledge therefore it would seem best to forgo any rigid attempt to differentiate cancer of the head from cancer of the body or tail of the pancreas For the time being, the better approach would appear to be an amalgamation of all the available data in an attempt to draw a composite picture of pancreatic cancer as it is encountered in office and hospital practice We have employed such an approach, first by reviewing the cases of cancer of the pancreas seen at the Graduate Hospital on the service of Dr Bockus, and second, by combining these data with similar data culled from the literature up to the time of our review The results of this study were reported in 1941 Studies made by other investigators since then have yielded remarkably similar findings In the tables to follow, a comparative listing has been made of (1) the averaged findings of the reports in the literature up to 1941 including the Graduate Hospital cases (2) the averaged findings in the Graduate Hospital cases and (3) the averaged findings in a recent series of cases reported from the University of Chicago by Dashiell and Palmer in the Archives of Internal Medicine of February 1948 The latter report was selected not only because it is one of the latest to appear but also because it is representative of other recent reports on this subject

GENERAL FEATURES

Considering the general features of the disease first (Table 27) it may be pointed out that cancer of the pancreas is a disease of rapid course with an

Table 27 General Features of Carcinoma of the Pancreas

	LITERATURE Includ G H Cases (To 1941)	GRAD HOSP 34 Cases (1941)	UNIV OF CHICAGO 90 Cases (1948)
Duration of symptoms (months)			
From onset to hospitalization	6 0	6 0	4 7
From onset to death	7 1	—	—
Age (years)	56 4	59 4	55 9
Sex			
Males	71	68%	—
Ratio males to females	2 4 1	2 1 1	2 1
Race			
Whites	71%	73%	—
Ratio whites to Negroes	2 5 1	2 8 1	—

average interval of six months from time of onset to hospitalization, and some seven months from onset to death It is a disease which involves dominantly the older age groups the vast majority of the patients being over 40

most closely in his mind and expected to find most often in patients with cancer of the pancreas Painless jaundice was selected as the outstanding feature by 43 per cent (Table 25) An additional 49 per cent favored jaundice without qualification as to whether or not it was associated with pain Hence, approximately 93 per cent of the group were of the opinion that jaundice, with or without pain but more especially painless, was the outstanding feature of carcinoma of the pancreas The bearing of these selections, and the trends of thought they reflect, on the problem of delay in the diagnosis of cancer of the pancreas will become apparent when the actual manifestations of the disease are reviewed

Any attempt to depict the clinical picture of pancreatic cancer, however careful, must at best be imperfect To begin with, the signs and symptoms vary depending upon the source of material For example, if the cases selected for review come from surgical institutions or represent patients operated upon, the incidence of jaundice may be expected to be high since jaundice is a symptom commonly leading to surgical intervention The

Table 26 Incidence of Involvement of Head in Carcinoma of the Pancreas

BASIS OF DIAGNOSIS	NO	%
Operative	87	93 1
Operative or necropsy	682	79 9
Necropsy	270	72 2
Not stated	410	88 5
Average		81 7

signs and symptoms vary also depending upon the portion of the gland predominantly involved by neoplasm Table 26 illustrates the variation in frequency of involvement of the head in pancreatic cancer depending upon the source of the material For example, in 87 cases in which the diagnosis was established purely by operation, the head was felt to have been involved in 93 per cent In contrast, in 270 cases in which the diagnosis was established at necropsy, the incidence of head involvement was only 72 per cent Yet, our clinical concept of the various signs and symptoms when the lesion is confined to the head, or to the body or tail, is founded to a considerable degree upon cases in which the site and extent of involvement were established purely and simply from operative observations

Another handicap is the repeated demonstration that some tumors which appear to have arisen in the pancreas prove instead to have their origin in the bile ducts or in other structures in the ampullary region Since the diagnosis in many cases reported in the literature was established on the basis of unconfirmed surgical observations, it is obvious that the data from which we must construct the clinical picture very likely contain inaccuracies

In the light of our present knowledge therefore it would seem best to forgo any rigid attempt to differentiate cancer of the head from cancer of the body or tail of the pancreas For the time being, the better approach would appear to be an amalgamation of all the available data in an attempt to draw a composite picture of pancreatic cancer as it is encountered in office and hospital practice We have employed such an approach, first by reviewing the cases of cancer of the pancreas seen at the Graduate Hospital on the service of Dr Bockus, and second, by combining these data with similar data culled from the literature up to the time of our review The results of this study were reported in 1941 Studies made by other investigators since then have yielded remarkably similar findings In the tables to follow a comparative listing has been made of (1) the averaged findings of the reports in the literature up to 1941 including the Graduate Hospital cases (2) the averaged findings in the Graduate Hospital cases and (3) the averaged findings in a recent series of cases reported from the University of Chicago by Dashiell and Palmer in the Archives of Internal Medicine of February 1948 The latter report was selected not only because it is one of the latest to appear but also because it is representative of other recent reports on this subject

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Ratio males to females	2 4 1	2 1 1	2 1
Race			
Whites	71%	73%	—
Ratio whites to Negroes	2 5 1	2 8 1	—

average interval of six months from time of onset to hospitalization, and some seven months from onset to death It is a disease which involves dominantly the older age groups, the vast majority of the patients being over 40

years of age Finally, it is a disease which predominates in males with a ratio of some 2 or 3 males to each female

SYMPTOMS

Among the symptoms characteristic of cancer of the pancreas, the outstanding ones in order of frequency are weight loss, pain and jaundice (Table 28) Weight loss is seen in about 9 out of 10 patients and probably is almost invariably present About 3 out of 4 patients complain of pain at one time or another during the course of observation Pain occurs more frequently when the body or tail is involved than when the head alone is

Table 28 Outstanding Symptoms of Carcinoma of the Pancreas

	LITERATURE Includ G H Cases (To 1941)	GRAD HOSP 34 Cases (1941)	UNIV OF CHICAGO 90 Cases (1948)
	Per Cent	Per Cent	Per Cent
Weight loss	87	90	80 (Prob 100)
Pain			
Initial symptom	50	—	—
Chief complaint	48	65	—
At some time or other	76	82	83
Jaundice			
Initial symptom	22	—	—
Chief complaint	30	35 (59)*	—
At some time or other	69	70	67
Painless jaundice			
At onset or on admission	18	26	—
Throughout course of observation	14	18	17

* Per cent noted to have jaundice on admission whether or not observed by patient

involved Even so, pain is still a common symptom when the cancer appears limited to the head A word might be said about some of the characteristics of this pain

First off, it must be emphasized that the pain of pancreatic cancer has no single special characteristic by which it may always be recognized Its character is variable It usually is constant and of a fair degree of severity It is most often situated in the upper abdomen and frequently radiates into the back *It tends to become exaggerated at night or when the patient is lying down* At these times the patient frequently must sit up lean forward or actually walk about the room stooped over to get some relief One other noteworthy feature is a tendency for the distress not infrequently to mimic

duodenal ulcer Indeed, duodenal ulceration may actually be associated with the disease, either as an independent lesion or secondary to invasion of the duodenum by the tumor

It will be noted from Table 28 that jaundice, the third most frequent symptom occurs less often than pain as an initial symptom, as a chief complaint and at some time or other during the course of observation Moreover, when both pain and jaundice develop in the same individual, pain precedes jaundice much more often than not As might be expected jaundice is seen less often when the carcinoma is confined to the body or tail than when the head is dominantly affected On the other hand, it should not be inferred that jaundice invariably appears when the head is involved by tumor Jaundice was not evident at any time in about one fifth of those of our cases

Table 29 Other Symptoms of Carcinoma of the Pancreas

	LITERATURE Includ G H Cases (To 1941)	GRAD HOSP 34 Cases (1941)	UNIV OF CHICAGO 90 Cases (1948)
	Per Cent	Per Cent	Per Cent
Weakness and fatigue	51	78	18
Anorexia	44	41	40
Nausea	34} 53	48	—} 27
Vomiting	36}	42	—}
Constipation	39	43	32
Diarrhea	11	30	20
Psychic phenomena	—	9 (11)*	7†
Venous thrombosis	30‡ {16 (head) 51 (body or tail)}	—	—

* When case previously reported by Yaskin is included
† Insomnia
‡ Sproul Dec 1938 and Kenney Oct 1943

in which the carcinoma was thought to be restricted to the head In almost half (49 per cent) of our nonjaundiced cases the carcinoma appeared to have extended into the head of the pancreas Similarly 42 per cent of Eusterman s and 38 per cent of Dashiell and Palmer s nonjaundiced cases showed involvement of the head

Jaundice without pain actually occurs in only a minority of the cases of pancreatic cancer As shown in Table 28 painless jaundice was noted in but one fourth of our patients when first seen and in many of them pain sooner or later supervened This relative infrequency of painless jaundice must be stressed since so many of the people polled by us selected it as the outstanding manifestation

The other symptoms which occur with a fair degree of frequency are shown in Table 29 Among them diarrhea deserves to be emphasized Not

only does this symptom occur with surprising frequency, but every now and then it is the heralding manifestation of pancreatic cancer Friedenwald and Cullen believed it occurs often enough to warrant the suspicion of cancer of the pancreas whenever persistent diarrhea is observed in a patient of middle life or older for which no adequate explanation can be found

Nervous, or perhaps more properly mental or psychic, phenomena likewise merit special mention As described by Yaskin, they consist principally of anxiety, an obstinate type of insomnia, depression with crying spells, and overwhelming fear of impending disaster Such symptoms are common enough and cannot be said to be specific or in any way limited to cancer of the pancreas Nevertheless, one would do well to look suspect upon them,

Table 30 Physical Findings in Carcinoma of the Pancreas

	LITERATURE Includ G H Cases (To 1941)	GRAD HOSP 34 Cases (1941)	UNIV OF CHICAGO 90 Cases (1948)
	Per Cent	Per Cent	Per Cent
Palpable liver	63	79	—
Palpable distended gallbladder			
In cases with jaundice			
Clinical	51	42	52
Laparotomy or necropsy	87	—	—
All cases			
Clinical	37	24	—
Laparotomy or necropsy	67	—	—
Palpable pancreatic mass	37	12	32
Ascites			
Preop or antemortem	16	12	—
Postop or postmortem	35	—	—

especially if they appear without obvious cause in an older person and more especially if they are associated with abdominal or back pain Too often pain in a person with such nervous symptoms is written off as a psychosomatic manifestation Its significance is not appreciated until jaundice makes a belated appearance

Still another noteworthy symptom is venous thrombosis Multiple venous thrombi appear to occur more often in carcinoma of the pancreas than in carcinoma in other organs This is particularly true of cancer of the body and tail

PHYSICAL FINDINGS

With respect to the physical findings in pancreatic cancer (Table 30), I would direct your attention particularly to palpable distention of the gall

bladder This finding is generally considered a classical manifestation of pancreatic carcinoma In about one half of the jaundiced cases a distended gallbladder may be palpated during ordinary physical examination A much greater percentage however, will be found to have a distended gallbladder at laparotomy or necropsy This would indicate that Courvoisier s law is indeed diagnostically useful, but it is especially useful to the surgeon exploring the abdomen in search of a primary lesion The significance and frequency of occurrence of the other physical findings are self-evident and need no special comment (Table 30)

LABORATORY FINDINGS

Anemia, while frequent is generally only mild in degree in cancer of the pancreas (Table 31) This is rather remarkable in view of the marked weight loss which is true of so many patients with this disorder

Table 31 Laboratory Findings in Carcinoma of the Pancreas

	LITERATURE Includ G H Cases (To 1941)	GRAD HOSP 34 Cases (1941)	UNIV OF CHICAGO 90 Cases (1948)
	Per Cent	Per Cent	Per Cent
Anemia	32	76	—
Average RBC	4 04 Mill	4 08 Mill	—
Average Hbg	76	69	—
Occult blood in stools	27	27	—
Fatty stools	10	4	—
Disturbed carbohydrate metabolism			
Glycosuria	9	24	27
Hyperglycemia	19	27	60
Impaired dextrose tolerance	21	78	86
Hyperlipasemia			
Preop	—	36	—
At some time or other	42	54	—

Fatty stools have long been looked on as still another classical manifestation of pancreatic cancer Yet fatty stools were surprisingly uncommon in our cases (Table 31) Even in the collected literature only 10 per cent of the cases were thought to exhibit fatty stools I daresay that were we more conscious of steatorrhea and were we to apply more exact chemical studies, the incidence of increased fecal fat would undoubtedly be greater than current data indicate The same applies to creatorrhea Accurate chemical

analysis for fecal fat has not been used as often as it deserves to be, largely because it requires an exacting technic and is time-consuming However, there can be no excuse for failure to use the very simple procedure described by Dorothy Andersen By this method, a stool sample is placed on a microscopic slide and stained with alcoholic solution of Sudan III or IV The fat content is then graded on a scale ranging from negative to plus four depending upon the amount of Sudan-stained fatty material seen per low power microscopic field If two or less droplets of fat stained by Sudan are present, the finding is considered to be negative, if half or more of the visible field appears Sudan-stained, the grading is plus four Negative and plus four readings are of distinct significance We have used this simple test and it has proved very helpful

A surprisingly frequent, but distressingly overlooked abnormality in carcinoma of the pancreas is disturbance in carbohydrate metabolism This may manifest itself as glycosuria, hyperglycemia or an impaired dextrose tolerance curve (Table 31) The latter is particularly revealing A diabetic type of dextrose tolerance curve may be found even in the absence of glycosuria and fasting hyperglycemia Nondiabetic patients with carcinoma situated elsewhere than in the pancreas may also display an impaired dextrose tolerance However, the bulk of evidence points to a significant relationship between diabetes mellitus and carcinoma of the pancreas so that derangement of carbohydrate metabolism in patients with this disease would appear to be especially frequent and of considerable significance

The importance of hyperlipasemia as a diagnostic sign in cancer of the pancreas has already been thoroughly described by Dr Johnson Over one third of our cases in which this determination was made showed an abnormal elevation before operation, over half of them showed such an elevation on at least one occasion throughout the course of observation (Table 31) Perhaps the value of serum enzyme determinations may be enhanced if estimations of the concentrations of these enzymes in the serum are made before and after the administration of pancreatic stimuli On the basis of observations made by them on experimental animals, Popper and Necheles have suggested that elevation of serum amylase or lipase concentration after a dose of secretin insufficient to affect the serum enzyme levels in normal persons would indicate partial obstruction of the pancreatic ducts, failure to observe an elevation in serum lipase or amylase after strong stimulation, such as by the use of a combination of secretin and one of the parasympathomimetic drugs, would indicate atrophy of the gland

Dr Lopusniak earlier described pancreatic secretory studies using duodenal intubation and various pancreatic stimuli Deficiency of external pancreatic secretion may be recognized by this method of study Additional information of real value in differential diagnosis may also be obtained The complete or almost complete absence of bilirubin in the duodenal contents before and after secretin indicates biliary obstruction at some point above the opening of the common duct into the duodenum Such a finding, coupled with evidence of intact external pancreatic secretion, would place the ob

structing lesion outside the pancreas and somewhere along the biliary tract proper

Cytologic examination of the duodenal contents after the method of Papanicolaou is a newer method of study that holds much promise in the recognition of pancreatic cancer At the recent meeting of the Eastern Section of the American Federation for Clinical Research Dr Brynes of Boston reported on his experience and that of his associates with this technic In 5 cases of cancer of the pancreas they observed unequivocal malignant cells in 2 We have been able to make a positive diagnosis of malignancy by this method of study in one case so far and plan to use it more extensively in the future

ROENTGENOGRAPHY

Roentgenologic examination, involving principally barium meal study of the upper gastrointestinal tract has proved to be one of the most valuable means of recognizing pancreatic tumor (Table 32) I must emphasize that the x ray findings are not pathognomonic of the disease They depend in

Table 32 Roentgenologic Findings in Carcinoma of the Pancreas

	LITERATURE Includ G H Cases (To 1941)	GRAD HOSP 34 Cases (1941)	UNIV OF CHICAGO 90 Cases (1948)
	Per Cent	Per Cent	Per Cent
Positive x ray signs	37	45	49

the main, upon encroachment of the tumor on neighboring structures Consequently roentgenologic examination is apt to be negative during the very early stages of the disease when diagnosis is most important but when the neoplasm has not yet attained sufficient size to produce compressive and infiltrative changes in the adjacent viscera Nevertheless, almost half of the patients examined roentgenologically by us and by the University of Chicago group gave signs suspicious of a tumor in or about the head of the pancreas The yield of positive findings may be expected to become even greater as experience increases and roentgenologists grow more alert to the disease

ENDOSCOPY

Gastroscopic examination may contribute information of value in the recognition of carcinoma of the pancreas Not only will it help exclude a primary intrinsic tumor of the stomach but it may disclose bulging or other defects in the stomach wall caused by an underlying pancreatic mass

The deep retroperitoneal situation of the pancreas precludes visualization of the gland through the peritoneoscope *Peritoneoscopy* however, may be

analysis for fecal fat has not been used as often as it deserves to be, largely because it requires an exacting technic and is time-consuming However, there can be no excuse for failure to use the very simple procedure described by Dorothy Andersen By this method, a stool sample is placed on a microscopic slide and stained with alcoholic solution of Sudan III or IV The fat content is then graded on a scale ranging from negative to plus four depending upon the amount of Sudan-stained fatty material seen per low power microscopic field If two or less droplets of fat stained by Sudan are present, the finding is considered to be negative, if half or more of the visible field appears Sudan-stained, the grading is plus four Negative and plus four readings are of distinct significance We have used this simple test and it has proved very helpful

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Question Does blood phosphatase have any clinical value in carcinoma of the pancreas?

DR BERK Hyperphosphatasemia may occur in the absence of hyperbilirubinemia in metastatic carcinoma of the liver In addition to this, an elevation in serum alkaline phosphatase is commonly seen in jaundiced patients with pancreatic cancer Under these circumstances, the elevation merely points to an obstructive basis for the jaundice It does not indicate the nature of the obstructing lesion

DR BOCKUS Be prepared for a shock This question reads Don t you know that medical students and young medical practitioners, having had very little experience of their own, repeat the error of their teacher

DR BERK As one having to do with medical instruction, I am painfully conscious that medical students reflect the teachings of their teachers Yet, in spite of everything we do to hammer these points home on cancer of the pancreas, I am afraid that were we to repeat the poll today the results would be quite similar I don t know why this should be unless it is due to the fact that we can t get our surgical friends to stop teaching students that painless jaundice is the outstanding symptom of carcinoma of the pancreas

Question What is your experience with parasympathetic block in acute pancreatitis?

DR BOCKUS We have not utilized this procedure in acute fulminating cases Dr Popper in Chicago some years ago reported relief of pain in a group of some 7 or 8 patients I believe Dr Groff injected several of our patients with recurrent relapsing pancreatitis I will ask Dr Groff our neurosurgeon who is going to talk about methods of relieving intractable abdominal pain this afternoon to give you his opinion concerning the value of paravertebral block in the relief of the pain of acute pancreatitis

Question Does tetraethylammonium chloride have any value in the treatment of acute pancreatitis?

DR THOMAS The effect of tetraethylammonium chloride is to block conduction in the autonomic ganglia so that as far as the parasympathetic is concerned it should resemble the effects of atropine In the pancreas atropine does not regularly diminish the volume of pancreatic juice, in experimental animals sometimes it even increases it In a certain number of human cases atropine has been tried with the idea of decreasing the hyper secretion that occurs in some cases of pancreatic fistula The reports were that it was not successful in these instances where the ordinary therapeutic doses were used

I think we can understand that when we realize that the effects of atropine become less and less marked as we go down the gastrointestinal tract I don t think that necessarily implies that atropine might not be used with benefit in acute pancreatitis or possibly even tetraethylammonium chloride because as Dr Bockus has pointed out it is desirable to limit the amount of

of some aid in differential diagnosis by identifying other intra abdominal lesions with which carcinoma of the pancreas may be confused Biopsy of a metastatic lesion accessible to the peritoneoscope may serve to establish the pancreas as the most likely primary site In occasional instances of obstructive jaundice where cholecystography is precluded, direct injection of opaque material into the gallbladder under peritoneoscopic guidance may be of distinct help Roentgenograms exposed after such a procedure may disclose an enlarged gallbladder and dilated biliary ducts and suggest pancreatic neoplasm by demonstrating an abrupt obstruction at the distal portion of the common duct

SUMMARY

In summary, then, this discussion has been concerned primarily with the need for and the means of arriving at an earlier diagnosis of carcinoma of the pancreas From the data considered, it seems clear that in order to achieve the goal of earlier diagnosis it is necessary for us, first of all, to raise our *index* of suspicion of the disease It is essential for us, next, to revise some of our ideas regarding its clinical manifestations We must appreciate the importance and frequency of pain and we must realize that while painless jaundice is of unquestionable diagnostic value, it is not characteristic of most cases In prosecuting diagnostic studies, we should take advantage of all the procedures currently available which are designed to show derangement in the internal and external secretions of the pancreas We must appreciate the value of roentgenologic examination of the gastrointestinal tract as a means of detecting changes in size and character of the pancreas Finally, we should intensiv ly utilize cytologic examination of the duodenal contents as a means of recognizing malignant cells which may have originated in the pancreas

It remains for the future to develop more selective tests of pancreatic function and to devise a means for rendering the pancreas radiopaque It remains for the future, also, to accumulate accurate data on proved cases of carcinoma of the pancreas from which it may become possible for us to pick out the earliest manifestations of the disease and clearly to differentiate lesions of the head from those of the body and tail

PANEL DISCUSSION

Question In what way is the glucose tolerance curve impaired in carcinoma of the pancreas?

DR BERK The glucose concentration in the blood following a test dose of glucose rises above the accepted normal level and shows a delay in return to the normal fasting level The curve is identical to that seen in diabetes mellitus

Symposium on Abdominal Pain

stimulation from other sources, such as the gastric secretion and the emptying of gastric contents into the duodenum, so it's entirely possible that atropinization, and tetraethylammonium, once we learn how to use it, might be useful in 'splinting' the pancreas

I can't answer whether tetraethylammonium would tend to produce shock I doubt if it would in the doses required, but that's something for the pharmacologist to determine

DR BOCKUS Have you had any experience with ephedrine? Does it decrease the volume of pancreatic secretion?

DR THOMAS We haven t had any experience, but in one report that I saw in which atropine was tried unsuccessfully, ephedrine was tried and found to be useful

DR BOCKUS I know some clinicians have favored its use in acute pancreatitis, but I have never seen very much experimental work in relation to pancreatic secretion

DR THOMAS I know of no data on experimental animals Epinephrine, of course, is known to inhibit pancreatic secretion but the effects are momentary as they are in all the other effects of epinephrine

REMARKS ON THE MECHANISM OF ABDOMINAL PAIN

HENRY L BOCKUS, M D

The topic, Abdominal Pain, is included in the course so that we may have the opportunity of briefly discussing the complaint which is most commonly responsible for patients visits to the abdominal diagnostician I appreciate that in the brief time available it is impossible to discuss in detail the complex mechanisms involved in the production of abdominal pain It is hoped that this brief discourse may arouse in some of you a renewed interest in this highly important topic

In thinking of pain it is well to have two general concepts in mind The first concept is well expressed by Hilton, Every pain has its distinct and pregnant significance if we will but carefully search for it This concept implies that pain is conservative and beneficent It is nature s warning signal that something is wrong It has been defined as the psychic adjunct of an imperative protective reflex With this concept in mind it should be mentioned that the clinician who is well trained in the interpretation of abdominal pain has at hand the most important single diagnostic aid in gastroenterologic diagnosis Well over 50 per cent of patients coming to the gastroenterologist have functional disorders Their presenting complaints must be carefully analyzed and appraised in relation to environmental, situational and personality factors

The second concept of pain to which I should like to draw your attention is that which has been stressed particularly by Rene Leriche, author of the book, The Surgery of Pain Pain soon loses its beneficent quality continuing beyond its period of usefulness Now it may become a disorder or disease in itself It becomes destructive—exerting a deleterious effect on the organism, setting up harmful emotional and body reactions Livingston, in discussing this quality, mentions that pain is a perception, as such it is subject to associated ideas, apperceptions, fears, etc This brings to mind the element of reactivity to pain its side reactions and the occurrence of secondary pains and secondary symptoms like nausea, vomiting sweating, chilling

THE APPRECIATION OF PAIN

In order to appreciate pain an adequate stimulus must be applied to an appropriate receptor apparatus Impulses are then transmitted over nerve fibers of varying diameters and at varying velocities The very large myelinated nerve fibers carry pain impulses at a speed as great as 100 meters per

distracting the patient, e g , by the clanging of a bell in his ear, or by having his mind intently concentrated on reading something in which the subject is keenly interested Pain threshold can be raised by hypnosis or by suggestion or by stimulating the sympathetic nerve pathways e g , by injecting epi nephrine Perhaps the pain threshold raising effect of a discharge of epi nephrine is the reason why pugilists do not feel keenly many hard blows and why soldiers who are injured do not seem to perceive pain to the extent that one would imagine considering the nature of their injuries, this is na ture s way of protecting us against intolerable pain

There are many factors which may lower pain threshold It can be lowered by apprehension or anticipation A pain that returns every half hour with regularity will be anticipated sooner or later and may seem more severe with each subsequent episode Conditioning may also lower pain threshold A pain which recurs in relation to some physiologic function or cycle may after repeated recurrences seem more intolerable and ofttimes it can be better localized Perhaps the most practical thing to remember about pain threshold is that inflammation of a part always increases the appreciation of a stimulus applied to that part This will be mentioned later

THE MECHANISM OF VISCERAL PAIN

Now a word about the mechanism of pain originating from a stimulus applied within the abdomen to a viscus The older students of pain mechanisms such as Harvey, Von Haller and Lennander, were convinced that the viscera themselves were insensitive to pain and that the visceral nerves con tained no pain fibers We know now that this concept is fallacious The viscera have the same type of nerve fibers that are found in the skin however, they are fewer in number and they have not been accustomed to the type of stimuli which are commonly applied to the skin, i e , they have not been conditioned as have the pain fibers of the skin Indeed in infancy the skin isn t so well conditioned either it is only after repeated stimuli have been applied that the young subject becomes able to accurately localize discomfort and clearly define its quality Certainly it may be said that normal viscera do not appreciate slight stimuli of the type which when applied to the skin are perceived as painful sensations For example one may touch the gastric or colonic mucosa with the finger, one may pinch it, or it may be subjected to a faradic current and no sensation will be perceived if the viscera are not inflamed But there is an adequate stimulant capable of initiating true visceral pain giving origin to impulses carried entirely over the sympathetic pathways, the adequate stimulus is increased intravisceral pressure caused by stretching, distention or contraction of the viscus This is the normal adequate stimulus for the initiation of true visceral pain Let us revert again to sensations ex perienced as a result of irritation of the gastrointestinal mucosa It has been inferred that a strong stimulus must be applied to the mucosa as compared with the skin, before sensation is produced For example in Wolf s experiments on the human subject with a gastrostomy, he demonstrated that if enough pressure (30 gm per square centimeter) is made with a glass rod

second, some of the very small unmyelinated fibers at a speed of only 0 5 meter per second This brings to mind the so called quick and slow pain with which all of us are familiar If you should strike your ankle against a desk or chair and you are alone, it is likely that you may say "damn it," because of the prompt sensation of sharp, bright pain You will remember that some time later (2 or 3 seconds) a second slower pain follows, perhaps the result of stimuli being aroused by slight tissue alteration due to the actual blow This brief illustration is used to bring to mind these two distinct types of pain which may be experienced following an appropriate stimulus

The second slower type of pain is usually termed *protopathic* Protopathic pain is the term used to describe pain which is not acute and bright, which is likely to be deep and diffuse, not sharply circumscribed, this is the type of sensation which best describes true visceral pain It is deep-seated and dull, nevertheless it may be very severe This type of pain returns first with regeneration of a cut nerve fiber in the skin

The other type of pain (like that experienced at once after a blow) is well localized and felt promptly after application of the stimulus This *epicritic* type of pain is experienced most often following insult to the skin because the skin has been trained by many previous experiences If epicritic pain follows a visceral stimulus, more often than not the stimulus is overwhelming, or the pain threshold is markedly lowered If it is the result of a visceral stimulus it is probably a type of referred pain due to severe inflammation of the viscus Usually epicritic pain does not occur as a result of a functional disorder as many true visceral pains do The clinical implications of referred and true visceral pain will be elaborated upon later

At this time it may be well to mention briefly our present concept of the *appreciation of pain* because we should always keep in mind the distinction between pain perception or pain threshold on the one hand and reactivity to pain on the other The neurophysiologists and pathologists like my friend, Dr Yaskin, in a sense are purists They tell us that pain threshold does not vary much from day to day in the same person and in different individuals as measured by the tests that are now available It should be borne in mind that most stimuli utilized for testing pain threshold have been applied to the skin The test most commonly mentioned is that in which radiant heat is applied to the uninflamed skin of the forehead The intensity of radiation which barely evokes pain is denoted the *pain threshold* (Schumacher, Wolff and Goodell) This represents an appreciation of the minimal stimulus capable of being perceived For practical purposes appreciation of pain comprises a much more complex mechanism We must accept the patient s word when he describes the character and intensity of pain We realize that in its appraisal we not only are obliged to take into consideration the description given by the patient but must form some idea of this patient s reaction to pain Th pain in itself, as has been mentioned, may set up various side reactions emotional and somatic, which taken together make the appraisal of pain at times exceedingly difficult Furthermore, pain threshold can be altered, as it was in the experiment mentioned previously The threshold was raised by

originating within the abdomen in which the sympathetic fibers do not participate Cerebrospinal nerve endings are present in the parietal peritoneum or just under it, some of these fibers extend into the roots of the mesentery and the posterior parietes Morley, the English surgeon, described this mechanism which is called the *peritoneocutaneous reflex* He discovered that stimulation of the dome of the diaphragm on the under surface caused pain to be referred to the region of the trapezius muscle the side of neck and the radial side of the arm The pain stimulus originated in the nerve endings of the phrenic nerve a cerebrospinal component, and the radiation occurred over cervical neurones with which the phrenic nerve communicates Similarly if other cerebrospinal nerve endings in the peritoneum or subperitoneal tissues are irritated, the communicating segmental somatic fibers may refer pain to a corresponding skin area This type of pain is often associated with spasm or guarding or rigidity of the abdominal wall muscles

It would appear, then, that at least three mechanisms may be called into play when pain stimuli originate within the abdomen (1) true visceral pain with impulses carried only via sympathetic fibers, (2) referred pain in which impulses are carried via both sympathetic and cerebrospinal nerve fibers and (3) peritoneocutaneous reflex of Morley, in which impulses are carried only via cerebrospinal nerves Perhaps it may be of interest to attempt to correlate theory with disease states One might explain the sequence of events from the standpoint of pain mechanism in cases of acute appendicitis as follows In acute obstructive appendicitis before the stage of inflammation, the viscus becomes distended The distention alone could account for the occurrence of the first protopathic type of pain which is experienced in the periumbilical or low epigastric area Nausea and vomiting may occur at this stage i e, the stage of true visceral pain in which impulses are carried over the sympathetic fibers only After a time inflammation ensues and sets up a bombardment of impulses over the sympathetic fibers These impulses are now more numerous and are being carried more rapidly over the afferent sympathetic pathways This should excite the secondary neurones in the cord and give rise to referred pain so that during this second stage of the disease referred pain may be experienced in the lower right abdominal quadrant Skin hyperesthesia and the so-called Head Zones of Tenderness may or may not be present The disease progresses Finally the cerebrospinal nerve endings become irritated as a result of the associated peritonitis and the peritoneocutaneous reflex of Morley comes into action This most intense pain at first is sharply localized to the site of peritoneal irritation At this stage muscle guarding or rigidity will be noted This most severe pain will be localized to the site of the appendix If the appendix is under the liver the pain will be in the upper right not in the lower right abdominal quadrant If the appendix is behind the cecum the first two pains, which often are not too severe may be difficult to appraise it is only with the advent of rupture and peritonitis that the significance of the pain in the right loin may become clear

The same sequence of events may occur in acute obstructive cholecystitis Certainly the first pain in acute cholecystitis is usually in the midline of the

against the normal mucosa, discomfort will result Less pressure was required to produce pain if the stomach was contracting at the time of making the pressure

As one might anticipate, a stimulus applied to a contracting viscus registers pain more promptly than a stimulus applied to a dilated one Wolf also obtained additional confirmation for the occurrence of lowering of the pain threshold in experiments on his human subject When this stomach was inflamed and congested, stimuli which ordinarily were not perceived (when the mucosa was normal) now were capable of causing pain This was true, for example, following pinching or by the application of the faradic current. There is now ample proof to indicate that the pain threshold is lowered by inflammation, that mucosal irritation which does not ordinarily cause pain will be perceived if inflammation exists, that sensations caused by distention and contraction of a viscus are intensified if the viscus is inflamed

There are at least three possible mechanisms which may be considered to account for pain occurring as a result of visceral stimulation The first is usually termed *true visceral pain*, i e , pain sensations caused by an adequate stimulus such as distention or contraction of a hollow viscus This type of pain occurs with exaggerated physiologic motor hyperactivity, it may be purely functional The entire reflex involved in the transmission of impulses may be via the sympathetic pathways The cerebrospinal nerves need not participate True visceral pain is likely to be protopathic Often it is not well localized, but is diffuse, deep and frequently vaguely situated in the midline If the stimulus is great, localization may be more striking However, in these instances it is likely that other mechanisms of transmission of impulses are present

A second mechanism called into play as a result of stimulation of visceral pain fibers entails participation of both sympathetic and cerebrospinal nerve pathways This is the mechanism of so-called *referred pain* By communication of afferent impulses (initiated in the viscus) via sympathetic fibers with somatic dermatomes, the pain sensation is referred to areas supplied by somatic nerves of the same segment in the cord MacKenzie and Ross explained this type of referred pain on the basis of creation of an 'irritable focus in the cord brought about by bombardment of a cord area with pain impulses brought by the sympathetic fibers It was presumed that normal impulses coming to the irritable focus would be translated into pain referred to skin areas which are in communication with the irritable focus This theory is not generally accepted The viewpoint of Hinsey and Phillips to explain referred pain has more support It assumes that both visceral and somatic afferent fibers carry impulses affecting a common pool of secondary neurones and that the principle of summation and inhibition is applicable Referred pain is usually sharp and epicritic and well localized It is likely that actual inflammation is present before this pain mechanism becomes active Radiation of pain probably depends principally upon two factors (1) strength of the stimulus and (2) lowering of the pain threshold as a result of inflammation

There is a third mechanism to account for pain as a result of stimuli

always give consideration to the origin of the tenderness in the abdominal wall itself as a result of a neuralgia

How do we differentiate between pain and tenderness limited to the abdominal wall from visceral tenderness, or from coexisting conditions where we have segmental neuralgia and visceral disease?

Imagine a patient before you for abdominal examination If with the abdominal wall relaxed you elicit tenderness, it may be either parietal or visceral Now have the patient tighten the abdominal wall by blowing out the abdomen raising the head or lifting the heels free from the table If tenderness is found then at least some of your original finding of tenderness is in the abdominal wall because you cannot get your fingers through the tensed muscles to feel the viscera However after this second test, there may still be some visceral tenderness

To complete the differentiation it is necessary to block off sensation in the anterior abdominal wall This can be done by paravertebral block with novocain or if below the level of the umbilicus by a local injection at McBurney s point, under the fascia of the external oblique

After the injection if a pinch of skin and superficial fat does not disturb the patient, then with abdominal wall tensed all tenderness of parietal origin should be gone If we now have the patient relax the abdominal wall and palpate again, we either find tenderness or no tenderness If tenderness is present, then visceral pain must be suspected but if all tenderness is gone, then all the tenderness found before novocain block was in the abdominal wall

Because this symposium of pain was limited to abdominal pain, I have constantly referred to the abdomen but let me call your attention to the fact that all parts of the body are covered by a layer of parietes rich in sensory nerves which may cause confusion when one is attempting to differentiate tenderness of superficial and of deep origin Let me repeat for the safety of future patients parietal tenderness and visceral disease may coexist

The causes of parietal abdominal neuralgia are many Usually it takes two factors to produce this confusing picture

In order of importance the causes are

1 Infection—usually above the clavicle
2 Trauma
3 Postural defect
4 Any combination of any two of the above and after that any tumor or disease affecting the spine and many of the metabolic disturbances

In those cases where no visceral lesion is to be treated, the segmental neuralgia must be treated to afford relief In those cases where both parietal neuralgia and visceral disease coexist after treating the visceral lesion the segmental neuralgia must also be treated in order to prevent a recurrence of symptoms which might prove misleading and be considered a complication of visceral disease It is this later situation that causes repeated unsuccessful and unnecessary operations

The cure or prevention of recurrence of parietal neuralgia is to find and eliminate the cause If infection is present it must be brought under control

epigastrium, not in the upper right abdominal quadrant This first pain is mild and protopathic in type, a true visceral pain, the result of distention of the gallbladder As inflammation develops, the more severe pain which follows is localized in the upper right abdomen and at times is referred to the right scapula This is probably an example of true referred pain in which both sympathetic and cerebrospinal pathways are utilized If the peritoneum be comes inflamed, then the third stage of very severe local pain and rigidity characteristic of the Morley reflex appears

Time does not permit the giving of further examples It has been possible only to give a brief outline of the possible mechanisms involved in the pro duction of abdominal pain I hope that it may stimulate a new interest in this very interesting and important subject

All abdominal pain is not the result of stimuli originating within the abdominal cavity Dr Bates will now discuss abdominal pain of parietal origin, so-called "Abdominal Parietal Neuralgia '

ABDOMINAL PARIETAL NEURALGIA

WILLIAM BATES, M D

In this symposium on abdominal pain, I want to call your attention to pain associated with tenderness Pain without tenderness is outside the scope of my presentation This combination of pain and tenderness coexisting in definite segmental areas, if attributed to parietal nerve stimulus, was originally discussed under the name of 'intercostal neuralgia Later we called it parietal neuralgia, and more recently ' segmental neuralgia "

We thought that my Chief, the late Dr J B Carnett, was a pioneer in directing attention to parietal causes to explain associated pain and tenderness in the abdominal area However, just before he died in 1934, we found an article by Franck of Germany written in 1895 This paper differentiated pain and tenderness in the abdominal wall from pain of visceral origin in a manner very similar to the description given by Carnett in 1926

More recently we found an article written by a Frenchman for admission to the French Academy of Medicine in 1846 that was similar to the two later papers I am certain that all three papers were the result of original thinking

The thesis presented by these three authors is that it is imperative when pain and tenderness are found in the abdominal wall, to differentiate them from tenderness which occurs as a result of disease of the underlying viscera

When tenderness is found during the course of the routine abdominal examination one may either consider disease of the underlying viscera, or of a mechanism capable of causing 'referred pain It is my belief that referred pain is practically never associated with tenderness and that one should

always give consideration to the origin of the tenderness in the abdominal wall itself as a result of a neuralgia

How do we differentiate between pain and tenderness limited to the abdominal wall from visceral tenderness or from coexisting conditions where we have segmental neuralgia and visceral disease?

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if trauma has been causative it must be treated and prevented if possible in the future If the cause has been postural, commonly a marked lordosis or scoliosis of the spine will be found

If lordosis is the prominent defect, Goldthwaite exercises to correct the lordosis are indicated When scoliosis is a factor and the spine is not fixed by previous disease, the probability is that one leg will be found to be shorter than the other This should be corrected by raising the heel on the short side Measurement can be made by x-ray with the patient standing, by steel tape measure, or by placing blocks of known thickness under the heel until the spine is straight

If pain and tenderness persist after correcting known lesions, paravertebral injections of the involved segments are tried The injections are of ammonium sulfate solutions If after three injections no lasting relief is afforded, the cause of the pain has probably been misinterpreted and the patient must be carefully reinvestigated

For the purposes of this afternoon's discussion, the important thing is to recognize the presence of segmental neuralgia to prevent unnecessary studies, needless operations and to afford patients relief of their symptom of pain

ABDOMINAL PAIN IN ORGANIC NEUROLOGIC DISORDERS

JOSEPH C YASKIN, M D

Abdominal pain due to organic neurologic disease is not common, and for that reason is occasionally overlooked The cause of abdominal pain in a great majority of cases is related to disease of the various abdominal viscera, and the clinician naturally seeks the cause for abdominal pain within the abdomen rather than in its walls However, abdominal pain may have its origin in the nerves of the walls of the abdomen or may be referred to that region from diseases of the spinal cord, roots and peripheral nerves In the interest of clarity, it may be well to briefly review the innervation of the abdomen

The walls of the abdomen, that is, the skin, the subcutaneous tissue, the muscles, the fascia and parietal peritoneum, including the diaphragm, are supplied by somatic sensory nerves from segments T7 to L2, and the diaphragm from cervical segments 4 and 5 Sensations arising in these structures, particularly pain, reach the parietal lobe of the brain by the following three neurones *Neurone 1 begins in the spinal ganglion in the intervertebral foramen* which sends an axone peripherally, which eventually becomes the intercostal nerve Another axone enters the spinal cord and terminates on the posterior horn cells The second neurone begins in the posterior horn cells, crosses in *the central portion of the spinal cord,* and ascends on the

opposite side of the cord as the lateral spinothalamic tract traversing the spinal cord, the medulla the pons, and midbrain, and ending in the thalamus The third neurone begins in the thalamus, travels through the internal capsule and eventually ends in the parietal lobe of the brain Other sensory *impulses beginning in the posterior spinal ganglion travel in the* posterior columns and in the anterior spinothalamic tract, and are probably not of great importance in the pain mechanism That portion of the first neurone which lies between the outer surface of the cord and the outer surface of the intervertebral foramen is known as the posterior or sensory root The structures distal thereto are designated as the peripheral spinal nerves

It is well known that the sensory supply of the visceral peritoneum and all the intra abdominal organs, hollow and solid, is furnished the sympathetic and parasympathetic divisions of the vegetative nervous system While these sensory nerves differ anatomically and physiologically from the somatic sensory nerves in that they are smaller in caliber, poorly or not at all myelinated, and transmit impulses at a slower rate, their course is the same as that of the cerebrospinal nerves namely, they are not divided into pre- and postganglionic fibers, they eventually enter the posterior roots and ascending spinal tracts through the spinal cord, neuraxis, and after a relay in the thalamus, to the cerebrum

Pain originating along the somatic nerves in the abdominal wall and diaphragm is no different from pain originating in the course of any other somatic nerves The pain originating in the viscera is more complicated It may result from an extension to the structure supplied by the somatic nerves such as the parietal peritoneum,[1] overdilatation,[2] or overcontraction[3] of hollow viscera and by stretching of the capsules of solid organs The pain may be referred to the abdominal wall in the form of viscerocutaneous and visceromotor painful reflexes[4 5 6] In addition Leriche[7] pointed out that the viscera have sense organs identical with those of the skin but that they are subjected only to intrinsic stimuli which even if they reach consciousness cannot be interpreted in terms of other sensations of external origin

The object of this presentation is to discuss pain that originates in the various parts of the cerebrospinal system, namely, peripheral nerves roots spinal cord and brain

ABDOMINAL PAIN ORIGINATING IN THE PERIPHERAL NERVES

This is uncommon Occasionally one sees abdominal pain resulting from direct blows to the abdomen, and the pain is really a result of contusion of the abdominal wall It is common knowledge that polyneuritis (neuropathy) both infectious and toxic rarely causes abdominal pain, unless the disease process involves the roots When neuritis does occur, it is accompanied by nerve trunk tenderness

The parietal neuralgias with segmental tenderness have already been discussed by Dr Bates They are important clinical entities to identify from the standpoint of treatment as Dr Bates has already clearly indicated

Occasionally one sees von Recklinghausen s disease involving the inter-

costal nerves This is readily recognized by the presence of the small tumors and other evidences of neurofibromatosis

ABDOMINAL PAIN DUE TO THE INVOLVEMENT OF THE ROOTS

This is more common than the involvement of the peripheral nerves Radicular pain is characterized by the following features (a) the distribution of pain is segmental or radicular in type and not peripheral, (b) the pain may be "mechanical" in origin, that is, brought out by the movement of the vertebral column, and may be increased by factors which increase intraspinal pressure or pull upon the roots such as coughing, sneezing, *straining at* stool, lifting, etc, (c) the pain is unaccompanied by nerve trunk tenderness but may rarely be accompanied by tenderness over the spinous processes and paravertebral regions

The roots may be involved by inflammatory processes, tumors, spondylitis and other causes The commonest causes are tabes dorsalis and neoplastic processes

TABES DORSALIS

As is well known, the degeneration and inflammation of the posterior roots is the primary process in locomotor ataxia Abdominal pain in the form of gastric crises is found in a considerable percentage of cases of tabes Indeed, they may be the earliest subjective manifestations of tabes, and are sometimes mistaken for an acute surgical abdomen Thus Nuzum[8] states that negligent examination accounted for 97 needless laparotomies among 1000 tabetics, while Woltman[9] reported 63 in a series of 120 cases of gastric crises The tabetic is seized abruptly with acute epigastric pain, seldom spreading to the shoulders or around the body The pain is anguishing and is accompanied by retching and vomiting of the stomach contents, and finally of bile or a watery mucus often streaked with blood The symptoms run for hours and days, producing marked exhaustion and dehydration Intense hyperesthesia develops over the pit of the stomach and sometimes in the back. Abdominal reflexes are usually overactive Gastric analysis reveals normal acidity or a temporary achlorhydria, or the reverse (Critchley and Wolfsohn[10]) X-ray films sometimes disclose pylorospasm and other abnormalities, even an appearance suggestive of ulcer, but *in crisis* cases they are liable to be misinterpreted (Fremont-Smith and Ayer[11]) An accurate diagnosis is nearly always possible *even in early cases* by the presence of pupillary changes, usually the Argyll-Robertson pupils, by the absence of the knee and Achilles reflexes, disturbances of deep sensations in the lower limbs, and in more than two-thirds of cases by the serologic studies

From a bedside standpoint, it is well to remember that a patient with tabetic crisis is restless, unable to keep still continually changing his position, often walking and even jumping in his attempt to relieve the pain As is well known, the patient with the acute abdomen ' tries to immobilize his body, especially his trunk, as much as possible I well remember many years ago making rounds and seeing a patient performing in a manner described for

the tabetic I jokingly said to the intern This woman behaves like a case of tabes dorsalis The intern informed me that ten days ago she had had a laparotomy for gallbladder disease but no pathology was found in the gallbladder The examination revealed small, stiff pupils an absence of tendon reflexes and marked diminution in position sense

ACUTE MENINGITIS

Occasionally acute meningitis, especially the meningococcic type in child hood may begin with severe abdominal pain as also occurs in pneumonia in children I have seen several patients admitted to surgical wards with diag noses of acute surgical abdomen that turned out to be instances of meningitis The routine neurologic examination, especially in children will disclose the rigidity of the neck and the Kernig signs, which when followed by a spinal tap, will lead to an accurate diagnosis

CHRONIC MENINGITIS

Occasionally one sees chronic meningococcic meningitis with pain in the renal region and in the abdomen The writer has seen one such patient who was studied in detail by urologists, and only when the urologic studies were negative was a spinal tap performed and it was found that the patient suffered from a chronic meningococcic meningitis

Abdominal pain is also seen, though rarely, in arachnoiditis which may be due to many causes and sometimes, unfortunately, follows spinal anesthesia

CHRONIC AND ACUTE SPINAL EPIDURAL ABSCESS

This is not an uncommon occurrence in Pott s disease and other forms of acute osteitis involving the lower dorsal and upper lumbar vertebrae The writer has seen patients treated for abdominal pain for long periods only to discover at autopsy an epidural collection due to unrecognized Pott s disease Patients are sometimes admitted to the hospital with severe abdominal pain and backache due to acute osteitis, often of undetermined etiology Not uncommonly the spinal epidural abscess when located in the lower dorsal or upper lumbar region is accompanied by considerable pain but of course evidences of spinal compression are usually found.

NEOPLASTIC PROCESSES

When the lower seven dorsal or upper two lumbar roots are involved by extramedullary tumors primary or secondary the first manifestations may be those of pain referred to the abdomen and more particularly to such areas as the gallbladder region and the appendix At times the presenting symptom is almost entirely abdominal pain and the other neurologic signs may follow weeks and months later

Two illustrative cases are of interest in this connection In one, a 60 year old man presented himself to Dr Bockus because of right upper abdominal pain Gastroenterologic studies were negative Some weeks later while at a health resort in the Middle West he was taken with severe abdominal pain

and returned to Dr Bockus with a diagnosis of gallbladder disease The pain was located in the dermatomes T7 and T8 A second enterologic study was again negative A neurologic examination about two weeks later revealed a right-sided Babinski reflex and a slight increase of the right knee reflex Bucky films of the spine revealed collapse of T6 and later studies disclosed that he had metastatic malignancy originating in the prostate gland He developed a Brown-Sequard syndrome and later a transverse myelitis

The second patient was a 36 year old man who complained of pain in the upper abdomen The first myelogram suggested a lesion at T5 A laminectomy was negative The patient continued having pain and became addicted to large doses of narcotics A reoperation three months later disclosed a neuro fibroma originating at T6 Fortunately, at the time of the operation the man had only a moderate compression of the spinal cord, made a satisfactory *recovery, and was relieved of his drug addiction*

While these cases are uncommon, it is well to bear in mind that radiculitis in the region of T7 to L2, and less commonly in the regions of C4 and 5, *may give rise to abdominal pain and that the routine neurologic examination* is most desirable in the study of abdominal disorders

ABDOMINAL PAIN DUE TO OTHER FORMS OF RADICULAR INVOLVEMENT

In addition to the causes already mentioned, one must remember that the various forms of spondylitis, vague or overlooked trauma, and toxic and infectious factors should be considered in the evaluation of abdominal pain Thus, in the so-called Guillain-Barre syndrome, radiculitis may cause pain in the abdomen

HERPES ZOSTER

This is an inflammation of the posterior root ganglion or of the posterior horn cells As is well known, there are two types—primary, which is infectious in origin and often follows epidemics of chickenpox, and secondary, due to the involvement of the structures surrounding the spinal ganglia in the inter vertebral foramina When the herpes zoster occurs in the region between T7 and L2, it gives rise to pain in the abdominal wall, closely simulating surgical conditions I have seen patients diagnosed and operated on for acute appen dicitis, only to find upon dressing the patients a few days later the charac teristic herpetiform eruption It takes from three to seven days for the eruption to appear after the onset of the abdominal pain, and it is not difficult to see that it may not be suspected, and be readily overlooked Depending on the location of the herpes zoster, many underlying organs may be held responsible for the pain until the eruption occurs

About fourteen years ago, the author began to have pain in the left upper quadrant Being a doctor, I did not see much sense in getting immediate attention since it was felt that if there was a neoplasm in the splenic flexure, there wasn't much cause for hurry A few days later I developed a herpetiform eruption and was chagrined because of my failure even to suspect shingles, even though my daughter had just recuperated from chickenpox

Among other causes of abdominal pain of unknown origin, it is well to think of shingles as one possibility

CENTRAL PAIN

By central pain is meant the type of pain that originates in the spinal cord or brain itself The author has never seen any intramedullary disease of the *spinal cord which produced significant abdominal pain Such a possibility is* conceivable Abdominal discomfort, vomiting and other gastrointestinal symptoms are common in the course of acute cerebral catastrophes, and in brain tumors with increased intracranial pressure There are those who believe that abdominal symptoms may be the initial or predominant evidence of *focal disease* of the brain There is some evidence that focal lesions in the diencephalon may produce gastrointestinal disturbances including abdominal pain [1] [13] Fulton[14] and others have shown that certain parts of the cerebrum are concerned with the innervation of the abdominal viscera Wechsler[15] and others observed a number of patients with brain tumors in whom the early symptoms were abdominal pain More recently a number of observers have believed that a good many cases of abdominal pain are in reality abdominal forms of migraine And lastly there are those who hold that abdominal pain may be a manifestation of the convulsive state The author has had no experiences with abdominal pain as a manifestation of focal brain disease

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SURGERY FOR THE RELIEF OF INTRACTABLE ABDOMINAL PAIN

ROBERT A GROFF, M D

Surgery for the relief of intractable pain is a destructive procedure since it consists of cutting spinal sensory nerves, sensory tracts in the spinal cord, or, within the past few years, the association fibers passing from the cortex of the frontal lobe to the median nucleus of the thalamus, otherwise known as prefrontal lobotomy Because these are destructive procedures and may be associated with certain complications, serious thought must be given to the total problem before recommending and carrying them out When the pain is caused by malignant neoplasm the problem is simple because the fate of the patient is known, the same may be said for gastric crises and various other chronic debilitating diseases On the other hand, when intractable abdominal pain follows more obscure conditions the problem becomes much more difficult, not only from the standpoint of recommending a destructive operation but also to determine what type of operation will relieve the pain In the light of this, it might be well to review for you the present status of our knowledge of referred pain

It is postulated that an essential factor in production of referred pain is the existence of branching among the sensory pathways conveying the sensation of pain This branching is of such a type that one limb of the branch axone passes to the site of origin of the disturbance and the others pass to the sites to which the pain is referred This mechanism works in two ways first, by leading to a misinterpretation on the part of the central nervous system of the true site of origin of the pain impulses, and secondly, by the liberation of metabolites at the terminals in the region where pain is experienced, thus giving rise to secondary pain impulses actually having their origin in the periphery In any given case both mechanisms are concerned, the first being initially more important than the second, but the second, that is the metabolite process, increasing in importance with time and in the later stages predominating I think, although I haven t heard Dr Bates paper, that he has given you an example of this by his discussion of parietal pain Yet these theories do not explain satisfactorily the role of the sympathetic nervous system unless one includes this system as a member of the sensory pathways That the sympathetic ganglia, splanchnic nerves and white rami communicantes play a role in pain conduction in the abdomen can be seen from the following data

PARAVEPTEBRAL BLOCK

Procaine block of the ninth and tenth sympathetic ganglia on the right side will relieve pain caused by gallbladder disease This procedure was first suggested by Burkman and carried out by Laewen in 1920 Subsequently,

Kappis Gurlock, Mandl and others have confirmed these results This work has been primarily foreign These same observers demonstrated that procaine block of the first and second lumbar ganglia would relieve the pain incident to renal disease when performed on the side of the pain Other sources of pain, such as stomach, pancreas and the other viscera within the abdominal cavity, have not been consistently relieved by the block of any certain sympathetic ganglia Pain arising from the stomach, for instance is apparently carried over the seventh, eighth, ninth and tenth thoracic ganglia bilaterally, and appendiceal pain is usually conducted through the first, second and third lumbar ganglia The value of these facts is that they serve as a means of differential diagnosis Pain incident to gallbladder disease can be accurately located and the same is true for renal disease

The procedure of blocking sympathetic ganglia is known as paravertebral block and I commend it to you for an aid in the differential diagnosis when the diagnosis is obscure At the same time, this type of procedure helps the neuro surgeon in determining what type of surgical procedure will relieve the patient of his pain

A word of caution must be injected at this point The procedure should be done by an experienced individual since one must know the indications and the contraindications as well as have a knowledge of the precise anatomy of the part Alcohol should never be used because it sets up at times a neuritis which is much more severe than the original pain

RHIZOTOMY

Turning now to the surgical procedures which are used for the relief of intractable pain, the first to be considered will be rhizotomy i e, cutting of the spinal nerves within the spinal canal Since most abdominal pain is produced by a sympathetic nerve involvement at least in the beginning it can be seen that rhizotomy is rarely useful in controlling abdominal pain An example of its effectiveness is in retroperitoneal carcinoma where you have direct involvement of the spinal nerve roots Rhizotomy will relieve most of the pain caused by lesions of this type

The operation consists of exposing and removing the lamina of the spinal canal, opening the dura and cutting the desired sensory spinal nerves Obviously the procedure may be either moderate or extensive and therefore, associated with mild or severe shock Needless to say, the operation is contra indicated in debilitated individuals The patient is left with a band of anes thesia the width of which is determined by the number of nerves cut Most individuals tolerate this well, provided the pain has been relieved

CHORDOTOMY

Chordotomy, that is cutting the anterolateral tracts which conduct pain and temperature sensations, serves a much more useful purpose in controlling intractable abdominal pain than does rhizotomy This remains true even though the pain impulses travel primarily over the sympathetic nervous pathways It is about 80 per cent effective in relieving intractable pain

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What are the effects of such an operation, other than the indifference to pain? The patient undergoes a definite personality change yet it is not as severe as that following bilateral prefrontal lobotomy Emotions are suppressed there is an indifference towards the family and friends, with a facetious trend almost simulating a jocosity in some patients The alterations of personality improve as the patient recovers from the operation but never disappear completely It can be easily seen that this form of surgery must be reserved for the incurable patient Since it can be performed under local anesthesia and is not attended with shock, unilateral prefrontal lobotomy can be performed in the patient who is ordinarily classified as a poor surgical risk

In conclusion, it should be remembered that the surgery of intractable abdominal pain is a destructive procedure and should be given serious thought before subjecting a patient to it Yet, on the other hand the procedures described should be used early before the patient is in complete desperation A good rule to follow is that, when an individual requires more than two doses of morphine per day, surgical procedures should be recommended for the relief of pain

PANEL DISCUSSION

Question If Sperensky s claims of curing disease by altering neural reflexes are legitimate, are there any explanations for the mechanics involved?

Dr Yaskin A D Sperensky, the Director of the Department of Patho physiology of the Old Union Institute of Experimental Medicine, published a book in 1934 called A Basis for the Theory of Medicine which was translated by C P Dutt in 1935 It so happened that I read it recently but I confess that I could not quite understand the thesis It covers the realm of medicine and is attempting to take into account the various etiologic factors and biologic processes to explain a great variety of diseases All his references with very few exceptions, are related to laboratory work done in the institutes in Mo cow, Leningrad, and some of the southern Russian universities I could not correlate his work with those of Sherrington, Langley and many others familiar to our culture Perhaps some day when on a long holiday or incapacitated and bedridden I may decipher some of the thoughts and understand them better

Question I have seen a mother and two daughters who had herpes zoster in the same location within six months The pain preceded the rash in all by ten days Will Dr Yaskin comment?

Dr Yaskin So far as I know there is no familial incidence of herpes zoster There are of course two types of herpes zoster—primary, which is a virus

The operation consists of removing the first two thoracic laminae, exposing the spinal cord and cutting the anterolateral tract on one side in the upper portion of the wound, and on the other side in the lower portion of the wound. The purpose of staggering the incisions is to prevent a transverse myelitis which results in paraplegia The extent of the cut, i e, the depth and the surface area, determines the height of the anesthetic level which should extend or begin from the toes up on to the thoracic cage, if it is to be effective in relieving abdominal pain In this area, only pain and temperature are destroyed The other modalities of sensation, touch, kinesthetic sense, etc, are preserved so that the patient can walk

The operation of chordotomy may be attended with two serious complications The first of these is *weakness of the leg* The pyramidal tracts are adjacent to the tracts which are cut and, if the cut is made too deeply, this complication will occur However, I think that our present technic has improved sufficiently that it is now a minor consideration

The second complication is *urinary incontinence* About 20 per cent of patients develop this complication following the operation As a means of prevention it has been suggested that the operation should be done in two stages, cutting one tract at each operation and staggering them about a month apart It is difficult to evaluate this method in my experience, because most of the patients who are referred to me for the relief of pain are in such a physical state that one cannot afford to take the time for a two-stage procedure

UNILATERAL PREFRONTAL LOBOTOMY

Within the past two years, unilateral prefrontal lobotomy has been used for the relief of intractable pain It was first reported by Scarff of New York At about the time of the publication of this paper, we began using the method and have to date about 12 patients who have been delivered from their intractable pain This operation does not actually relieve pain in the sense that one relieves pain by cutting a sensory nerve or root The effect is one of taking away the patient's suffering and reaction to pain To illustrate this more clearly, if the patient is asked how he feels, he will respond "all right," "fine," or a similar expression If he is asked whether he has pain, he answers "Yes" and further quizzing will bring out the fact that it is of the same character and in the same location as before, yet his thoughts can be readily diverted from it These patients do not require sedation, nor do they show the physical reaction to pain

The operation is performed in several ways I favor the direct method, that is, making an opening in the skull about 1½ inches in diameter just in front of the coronal suture and making an incision in the frontal lobe by direct vision With this method, the possibilities of postoperative hemorrhage are much less

It would seem from the evidence thus far that it makes little difference upon which side of the brain the operation is performed I prefer, however, to use the dominant hemisphere, feeling that I am more likely to obtain the desired result

dorsal spine by an elevator on the operating table during cholecystectomy Very severe back and abdominal pain was observed to follow this procedure in several of my patients with arthritis

Question How frequently is abdominal myositis due to rheumatic fever seen in your clinic?

DR. YASKIN I have never seen it in rheumatic fever except in a child who was admitted to the hospital with a diagnosis of an acute surgical abdomen, and who had acute rheumatic fever with a pericardial effusion I have seen acute cerebral disturbances including strokes as the earliest manifestation of a rheumatic state Thus a youngster of 13 suddenly developed a left hemi plegia On admission to the hospital no murmurs were audible to anyone except Dr George Griffith but a month later the mitral murmurs were quite distinct

The only case I remember is a pericardial effusion with enough abdominal pain to consider the diagnosis of an acute abdomen

DR BOCKUS In rheumatic fever, changes may occur within the abdominal cavity that may give rise to pain simulating appendicitis and gallbladder disease I have observed this on several occasions In recent years we have had very few instances of rheumatic fever in the Graduate Hospital

Question What do you recommend for the relief of intractable and continuous pain as the result of chronic pancreatitis perhaps associated with calci fication? What procedure would you recommend and, if more than one in what order?

DR GROFF It is known that at least some of the pain arising from pancreatic disease is conducted over the sympathetic nervous system more specifically the thoracic ganglia T8–10 on the left My plan of management would be to block these ganglia with procaine If the pain is relieved depending on the length of time I would either reinject or recommend surgical removal of them with the splanchnic nerves

DR BOCKUS What are the results?

DR. GROFF As far as personal experience is concerned, I have none According to Poppen he had good results in 2 out of 5 patients The diag nosis in each was acute pancreatitis and not the chronic variety about which you are concerned

DR. BOCKUS You believe then that the pain impulses are entirely over the sympathetic nervous system?

DR GROFF Primarily yes There is a distinct possibility in connection with the branched axone theory that some of the fibers for conveying pain are a part of the sensory system It may be that this theory accounts for the unsuccessful results reported by Poppen

DR BOCKUS I am wondering whether by attacking the sympathetic nervous system only a high percentage of cures will be effected In those patients where the pancreas has been inflamed many times a great deal of posterior peritoneal inflammation has taken place One wonders what proportion of

infection and for many decades was known to be associated with chickenpox, and the secondary type, which is due to disease of the ganglia and the posterior horn cells

DR BOCKUS It is my impression that Dr Stokes here in Philadelphia has indicated recently that the virus of chickenpox and that of herpes zoster are practically identical in their morphologic characteristics

Question Have you any experience with tabetic abdominal crises as a complication of pernicious anemia?

DR YASKIN I have seen pernicious anemia associated with tabes dorsalis, but I have not seen tabetic crises as a complication of pernicious anemia Pernicious anemia is a disease of the posterior and lateral columns It is not a disease of the roots The roots are slightly, if ever, involved Therefore, tabetic crises occurring in pernicious anemia are not related to that disease In pernicious anemia, especially in neglected cases, one observes neuritic and neuralgic pains, but they are not a conspicuous feature in the course of these cases

Question What is a good text on the interpretation of pain?

DR YASKIN I can recommend the book by Livingston Leriche's book, of which there is an excellent translation, and which is about ten years old, is still a very good book, Mackenzie s book for those who have lots of time and are scholastically minded is very good

DR BOCKUS I can recommend the new monograph on 'Pain' recently written by Stewart Wolf and Harold Wolff It is a nice introduction to the subject and can be read in an hour and a half There are several very valuable chapters on the mechanisms of abdominal pain in the book 'Autonomic Nervous System by White and Smithwick

Question Why be careful with the use of novocain in patients with large pupils?

DR YASKIN I'm not much of a pharmacologist, but people who have dilated pupils are presumably sympathicotonic, in other words, they are individuals who are sensitive to such drugs as epinephrine, and for that reason cocaine may affect them very adversely But that isn t always true

Question How often do you get abdominal pain in the course of arthritis of the dorsal spine and upper lumbar spine?

DR YASKIN I haven t seen much of it I suppose it does occur but the fact remains that in severe spondylitis, especially spondylitis rhizomelique, where the spine is ankylosed, there is little abdominal pain, but that it may occur I have no doubt I can readily understand that, but it s not a conspicuous feature Backache is by far more common

DR BOCKUS I think there is no doubt concerning the occasional occurrence of abdominal pain when the arthritic spine is subjected to some stress This impressed me many years ago when it was customary to raise the lower

dorsal spine by an elevator on the operating table during cholecystectomy Very severe back and abdominal pain was observed to follow this procedure in several of my patients with arthritis

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CLINIC—NARROWING OF PYLORUS

GRADUATE HOSPITAL STAFF

Dr Robinson We would like to present to you this afternoon a problem that we had in September of this year in a sixty three year old white woman who was admitted to the hospital complaining of loss of appetite indigestion and upper abdominal distress This woman had been well all of her life until 1939, at which time she had abdominal symptoms characterized principally by upper abdominal pain not recalled well enough to give us specific details It was not associated with nausea or vomiting and jaundice was not a characteristic of this episode She had been hospitalized at another hospital where a diagnosis of cholecystitis was made A gallbladder stone was recognized on the flat film of the abdomen and serious consideration was given to cholecystectomy at that time However her pain subsided she was discharged from the hospital feeling well

She remained free of symptoms until 1944 when she had a back injury which was described as a fracture requiring a cast for four months, after which she had been essentially free of back pain

In May of this year she had her first definite gastrointestinal symptoms aside from the isolated experience of pain in 1939 She began to notice a vague sense of fullness and upper abdominal pain which she had first associated only with the ingestion of foods which were sour, spicy or fat She attempted therefore, to restrict her diet but despite these restrictions she noticed the continuation of regularly recurring postprandial distress in the mid epigastrium and she found that milk relieved this No other measures afforded relief and she did not experiment with medication The discomfort had no relation to change of position or to bowel habit There was no belching nausea or vomiting She found that she was being regularly relieved if she took a glass of milk between meals

Sometime during the summer she began to notice the insidious onset of anorexia She had heretofore had a fairly hearty appetite and was able to eat anything until she began restricting her diet in May For a month prior to her admission she began to notice occasional dysphagia This was a little difficult to evaluate because she found that she had no dysphagia when she ate food that she liked particularly green vegetables and salads With other foods there was a sense of some difficulty in swallowing and it required some amount of fluids with meals to get through the meal comfortably She gave a vague history of some increasing satiety with meals but that was a little difficult to appraise She said she was satisfied with less food, but it was

reactions for occult blood were negative No HCl was found in the fasting residuum At the height of the secretory curve after the Ewald meal there were 25 units of HCl and 64 units of total acid A Papanicolaou stain was made of the gastric sediment and was interpreted as an equivocal finding, it was not a positive test The electrocardiogram indicated some evidence of mild myocardial damage with right bundle branch block Sigmoidoscopic examination was reported as showing a slight nutmeg appearance of the colon which was examined for 10 inches, it was felt this might represent early melanosis coli The mucous membrane was otherwise normal

The patient was placed on hourly feedings, using a formula consisting of 80 gm of skim milk powder and 80 gm of dexin, in 1 liter of whole milk,

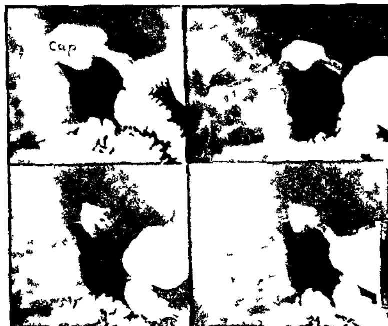


Fig 164 Serialgram (preoperative) showing pyloric narrowing September 16 1948

and was given 5 ounces of this mixture hourly from 7 A M until 9 P M No antacid was used phenobarbital 1/2 grain tablet was used three times a day After our initial studies were returned, additions to the diet as soft cooked eggs, cereal, toast and puddings, were made

This woman was not seen in our clinic as an out patient She had been referred to the hospital by one of the staff men who had had some x-ray work done on the outside because of her complaints This was done at another hospital in the city where she is employed

Dr Finkelstein These are the most important films made before she came to us, they were made on August 26 showing the elongated narrowing of the prepyloric region extending for a distance of perhaps 1½ inch The narrowed lumen is smooth in outline a trace of the mucosal pattern is visible

difficult to quantitate the amount of satiety she had Her bowel habit had been regular and unchanged during this period of time, she experienced no severe paroxysms of pain Occasionally late in the evenings she would have recurrence of the same type of pain which again would be relieved by milk She was characteristically free of pain during the night, continued to sleep well during this period of time There had been no loss of weight during this period of four months

In her past history, she denied any serious illnesses, she denied typhoid fever, she had been married but her husband had died twenty years ago, she had had no pregnancies

In the system review it was noted that she had occasional minimal dysuria in association with upper respiratory infections Recently she had had increasing nocturia up to four times Her menopause occurred at the age of 50 years and was uneventful Her habits were regular, she used neither alcohol nor tobacco, had regular hours of sleep and of eating She had been a dressmaker for the past twenty years

Her family history was interesting in that a mother had carcinoma of the stomach, a sister had died of carcinoma of the spine, the primary site was not known

On physical examination her blood pressure was normal (140/80), she weighed 157 pounds and stood 5 feet 2 inches in height She was well nourished, slightly obese The general physical examination was essentially normal In the abdomen the liver, the spleen and the kidneys could not be felt There was tenderness particularly in the sub-xiphoid area but also some tenderness was noted in the upper quadrants Normal bowel tones were heard, no mass could be detected, the sigmo colic junction could be palpated but was nontender She had no abdominal scars Rectal examination was negative Pelvic examination reported ultimately by the gynecologic service revealed "senile vaginitis, otherwise a normal pelvis' No adenopathy was detected She was afebrile and remained afebrile while she was undergoing a course of study on the medical service

The following pertinent laboratory data are mentioned She had 4,120,000 erythrocytes, 12 gm of hemoglobin, 6400 white cells, 76 per cent neutrophils, 22 per cent lymphocytes, this was representative of repeated counts done in the course of her hospitalization Sedimentation rate at the time of admission was 13 mm (Westergren, 1 hour), prothrombin time was 15 seconds which was reported as 50 per cent of normal, blood sugar, 82 mg, urea, 19 mg, total protein 7 52 gm with 3 79 gm of albumin, cholesterol was 272 mg, the ester fraction being 172 mg The serum bilirubin was less than 0 2 mg by the photoelectric colorimeter determination The bromsulfalein retention was 6 per cent at the end of forty-five minutes using the 5 mg dose The liver flocculation tests including the cephalin, thymol, colloidal gold and scarlet red tests were all normal, urine urobilinogen was positive in a dilution of 1 10 Random samples of her urine showed a specific gravity ranging from 1 006 to 1 025, no albumin, no sugar, microscopy was normal Three stool examinations were sent over for routine analysis and were essentially normal,

that of this patient The symptoms were those of a mild type of pyloric obstruction He explored her with the idea that the lesion was malignant Dr Erb found a typical smooth hypertrophy of the pyloric muscle completely encircling the pylorus He did a Ramstedt type of procedure, a longitudinal splitting of the muscle permitting the mucosa to bulge through She felt somewhat better for two or three months, then her symptoms recurred Roentgen study revealed a pyloric narrowing identical with the preoperative study In addition at this time a defect was noted on the posterior wall of the stomach higher up This was suspected of being malignant

We then explored the patient again, about four months after the first operation We could see where the incision had been made in the pyloric muscle It had not retracted very much, the thickened pyloric muscle was still present and certainly was compatible with the x-ray findings In addition to this, she had a large ulcer on the posterior wall, which had perforated into the lesser peritoneal cavity We did a resection and the question arose in our minds whether the pyloric narrowing had been responsible for the initial symptoms or whether the large ulcer had been present originally At any rate the symptoms disappeared for two months after dividing the muscle In the other patient it was not possible to differentiate at operation between actual hypertrophy of the pyloric muscle and malignancy The lesion proved to be a tremendous hypertrophy of the pyloric muscles

Dr Bockus Dr Dapena, do you believe that it s possible for the surgeon to tell by palpation whether or not the pylorus is pathologically thickened?

Dr Valdes-Dapena Aside from the stenosis resulting from peptic ulcer, we recognize pathologically three types of organic pyloric stenosis

(1) Neoplastic
(2) Hypertrophic
(3) Non specific benign pyloric stenosis

The first two are self explanatory The neoplastic type is frequently encountered with any type of infiltrating carcinoma In the submucous type the diagnosis may have to await microscopic studies The hypertrophic pyloric stenosis which is well known to pediatric surgeons is encountered now and then among adults and has to be considered in the differential diagnosis

The third category probably includes a variety of pathologic entities Non specific benign pyloric steno is was known as far back as 1829 and it was then that the equivocal term of benign pyloric hypertrophy was coined In general the lesion falls within the limits of an inflammatory type of reac tion The inflammatory elements may involve the muscle giving an appearance of hypertrophy it may primarily affect the submucosa in the form of edema with more or less fibrous proliferation Finally many observers found a good deal of thickening of the serosa and considered that the chief lesion Naturally various combinations of these changes have been reported

In regard to the interpretation of these pathologic findings some have attributed them to a localized gastritis, a form of linitis plastica which affects only the pyloric region It has been called an interstitial gastritis Again

at the proximal margin of the defect There is a concave configuration of the base of the duodenal cap At this time when the barium is not actively flowing through the pylorus, only a thin stream of barium is seen but one can see that the lumen of the narrowed segment is moderately distensible As far as I know at this time, there was no delay in gastric motility I do not know what diagnosis was made on the basis of these films, taken elsewhere

Our films made about three weeks later on September 16 show essentially the same extent and degree of smooth narrowing of the prepyloric area and at times a similar concavity at the base of the duodenal cap (Fig 164) Gastric motility was definitely normal at this time, the stomach being empty at the end of two hours This region, the pyloric and prepyloric areas, as well as the duodenal cap, was normally mobile on palpation under the fluoroscope We have the usual films of the rest of the stomach and of the duodenum in which we were not able to identify any pathology

From the roentgen standpoint, we could do little more than point to the objective signs of pathology without reaching a conclusive diagnosis except *to indicate that the narrowing, in our opinion, is organic We felt that it* could not be attributed to regional spasm in view of its persistence and length There is no evidence of an ulcerating lesion at this site nor is there any deformity visible which would indicate the presence of a previous ulceration It was our feeling that this might represent a hypertrophic muscle in the pylorus and prepyloric area, but that it might also be due to fibrosis resulting from the presence of a healing or healed benign ulcer, or a benign or malignant neoplasm, intrinsic in the stomach

Dr Bockus Do any of you believe that it is possible to make this differential diagnosis? Evidently there is general agreement that it is not possible by roentgen methods to differentiate submucosal scirrhous malignancy, benign tumor of the pylorus cicatrix from previous pyloric ulcer and benign pyloric muscle hypertrophy Dr Robinson, will you tell me what your chief decided at this time concerning the diagnosis and the course to pursue

Dr Robinson We made a presumptive preoperative diagnosis of a scirrhous carcinoma in the prepyloric segment We felt this diagnosis could not be excluded by clinical means and that exploration was warranted We knew that the patient had a stone in her gallbladder which probably had nothing to do with her symptoms She was referred to Dr Ferguson s service with the thought that a partial gastrectomy would be required

Dr Bockus Is there a representative from Dr Ferguson s surgical service here?

Dr Smith Dr Ferguson explored this patient expecting to find a malig nant lesion, but none was found The pylorus seemed normal to palpation It did not seem to be thickened The only pathology detected was a thickened gallbladder containing a stone He then did a cholecystectomy and closed the abdomen feeling quite confident that the pylorus was normal

I have had a very limited experience with this condition, but I have seen two patients with similar roentgen defects, if I may tell you about them One was a patient of Dr Erb The roentgen appearance was almost identical with

least as great as it was preoperatively In fact I think that few of you would doubt that the defect is actually perhaps 25 per cent longer The degree of narrowing is unquestionably greater in the postoperative study This is indicated not merely by the delay in initial emptying of the stomach or the narrow column of barium, but is indicated also by the retention of barium in the stomach to the extent of perhaps half the meal six hours after its ingestion

You will recall that preoperatively there was no delay in gastric emptying, the stomach having emptied two hours after the meal It is somewhat difficult to interpret this change from the roentgen standpoint In fact, I am not able to offer any definite explanation for it except to say that it is apparently more of the same process which was present prior to operation

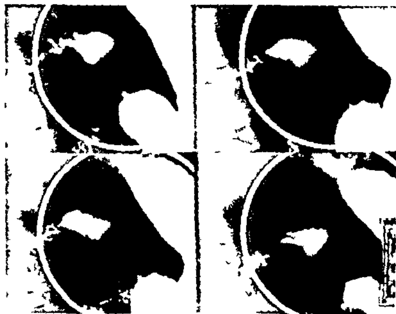


Fig 165 Serialgram (postoperative) Narrowed segment seems longer October 29 1948

Dr Bockus Do you mean more spasm?

Dr Finkelstein I didn t say spasm

Dr Bockus Have you ever seen this configuration of narrowing of this length due to a spasm? Evidently not Then how can you explain the fact that the surgeon could not feel something at the time of operation and that now the lesion has increased in length? Do you think it is a growth or do you think it is muscle hypertrophy, Dr Finkelstein?

Dr Finkelstein I don t know I do not believe much in muscle spasm or spastic phenomena to account for a constantly demonstrable constriction of this length anywhere in the digestive tube though I realize that perhaps it can happen I would suspect that whatever the underlying organic pathology

those who have noted particularly the serosal inflammation seem to have found the disease in association with other serosal changes and have attempted to establish a connection with polyserositis

The literature in this country has not dealt to any extent with this type of pyloric lesion We have seen in our surgical material definite cases of chronic inflammation affecting the pyloric mucosa as well as the gastric wall in that area, but we have not correlated them with the clinical picture or radiologic findings of pyloric obstruction Of possible interest is the fact that frequently edema predominates rather than actual inflammation, in that eosinophilic infiltration is often striking Without attempting to set down a new theory we might suggest that such changes might be of a chronic allergic nature

From the clinical standpoint it is important to stress once more that the gross characteristics of any pyloric stenotic lesion may be very suggestive of carcinoma and that the latter may simulate the clinical features of any of the above-mentioned benign lesions Unless surgery is undertaken for diagnosis the study of gastric secretion for cancer cells may be of great importance in some cases

DR BOCKUS I believe I will be able to convince you, Dr Dapena, that there is only one thing to do when you see an x-ray film showing this type of pyloric narrowing Incidentally, concerning your description of lesions of this type in association with chronic gastritis, etc, we do not see such lesions very often giving rise to the type of smooth narrowing seen in this case I'm not so sure that some of the older literature that you have quoted can be relied upon for accuracy When you encounter a defect like the one under discussion in the pylorus usually it means one of two things, either pyloric muscle hypertrophy or tumor The submucosal lesions causing defects of this type usually turn out to be adenocarcinomas, particularly when they are so circumscribed I should like to repeat a question Do you believe that a degree of thickening similar to that noted on the x-ray films should always be obvious to the surgeon without opening the stomach?

DR DAPENA I think this lesion should be thick enough to be palpated

DR BOCKUS Dr Robinson, what has happened to this patient?

DR ROBINSON She had a very uneventful postoperative course Dr Ferguson, at operation, palpated the entire pylorus very carefully and he could find no abnormality there The thumb which he had inserted against the duodenal cap area and the index finger which was introduced through the prepyloric area were brought together He satisfied himself that there was a perfectly adequate lumen, there was nothing noted grossly to warrant a radical procedure Therefore the cholecystectomy was done, she had a smooth postoperative course, being discharged from the hospital seven days post operatively I saw her in the clinic two weeks after discharge from the hospital and we arranged to have her first postoperative follow up study of the stomach and duodenum and we will show those films now

DR. FINKELSTEIN This is representative of the study made about five weeks following operation (Fig 165) At the end of one hour none of the barium had left the stomach The extent of the prepyloric narrowing is at

traction and relaxation of the normal pyloric muscle It will be our first case if it turns out to be spasm of the normal muscle

Dr Robinson The patient was able to return to work three weeks after her discharge from the hospital She had spent a two week vacation living with her sister, and she was really anxious to get back to work She was noticing just a little fatigue and was not completely free of the symptoms that she had preoperatively She is free of the epigastric distress Her weight is maintained The gastric analysis has not been repeated yet She is taking no medication She was advised to follow a low fat diet after the cholecystectomy but she is essentially on a full diet now



Fig 166 (February 2 1945) Spot roentgenogram showing elongated and narrowed pars pylorica Note the normal appearance of the duodenal bulb and the absence of cuffing at the proximal end of the narrowed area

Dr. Bockus At this time I think it might be of interest to hear from Dr Berk who has had an experience somewhat similar to the one under discussion

Dr Berk The case history I would like to present is that of a soldier, thirty two years of age when I first saw him in January, 1945 His symptoms were then of about two years' duration They comprised anorexia, slow but progressive weight loss, irregularly occurring vomiting and a substernal burning sensation About three months prior to his admission to the hospital where I was stationed an additional symptom had appeared This consisted of poorly described midabdominal pain appearing about one hour after meals and lasting for three and as long as four hours There was no distinct food ease pattern associated with it At about the time it first appeared, he had a single tarry stool which left him weakened for a short period

On admission to the hospital he was ambulatory and did not appear either

proves to be, and which I would now think is muscle hypertrophy, it has progressed

DR BOCKUS I was wondering, Dr Dapena, since the defect has increased in length and since the surgeon did not feel it, whether there would be a slightly increased chance that the lesion is neoplasm rather than muscle hypertrophy I wonder whether there would be more of a chance of not being able to palpate a very early submucosal neoplasm than pyloric muscle hypertrophy?

DR DAPENA Certainly the lesion could be submucosal, it may be a scirrhous neoplasm Could this be rugal hypertrophy *of the mucosa in that area?*

DR BOCKUS I've never seen hypertrophied rugae causing a long narrow defect of this type in the pyloric canal I am sure of one thing, that is, I am unwilling to take the responsibility for having this patient go on I feel that she should be subjected to a gastric resection without further delay If the surgeon wants to take that responsibility, he may, but I won't take it because I have never seen a lesion of this type that did not turn out to be an organic lesion—either pyloric hypertrophy or tumor, or a rare instance of a circumscribed inflammatory lesion This is a very interesting problem because the patient has been explored by an expert surgeon who felt nothing If the lesion is found to be marked pyloric muscle hypertrophy, it will be an amazing lesson because one would think that thickening of this degree could be palpated Dr Berk in a moment will have something more to say about this phase

(*Question*) Can such a defect be caused by Hodgkin s or similar infiltration of the prepyloric area?

DR FINKELSTEIN Yes, I see no reason why not Hodgkin's disease can imitate, as far as I know, any neoplastic process as far as the roentgen appearance is concerned, but that is not the question here *It seems to me that from* the roentgen standpoint, at least to my mind, there is no question but that there is an organic lesion, and it is not my responsibility if the surgeon can't palpate it That s the whole crux of the matter

DR BOCKUS The differential diagnosis of this lesion is not going to be made unless it is examined histologically Personally, we have had very little experience with Hodgkin s disease of the stomach I have seen 3 instances, none of them produced roentgen defects resembling this one The involvement has always been more diffuse The lesions were higher in the stomach and in every instance there were associated ulcerations Obviously, it cannot be excluded with certainty any more than other rare lesions like leukemia, syphilis or tuberculosis can be excluded

(*Question*) Were antispasmodics tried during the course of the roentgen study?

DR BOCKUS No, we have never seen a defect of this type clear up on antispasmodics

Dr Berk will discuss in a moment the question of the effect of relative con-

the operation A sizable adhesion was found which extended from the lesser curvature of the antrum to the liver The stomach itself was considered entirely normal The surgeons hypothesized that with the stomach filled, as with barium during roentgen study, the resultant downward drag would be counteracted by the nonyielding adhesion, thereby producing pseudo narrowing of the distal stomach The adhesion was lysed and, only because I kept annoying them, the stomach opened and explored A longitudinal incision was made in the anterior wall of the antrum just above the pylorus The interior of the stomach was inspected through this opening and found to be entirely normal in appearance A thin slice of the entire stomach wall was taken from one side of the opening and the incision then closed transversely so that the entire procedure constituted a form of pyloroplasty



Fig 168 Histopathologic section of biopsy taken from pyloric portion of stomach at surgical exploration on March 14 1945 A small area of mucosal denudation may be seen. The striking finding is noninflammatory thickening of the muscle

Histopathologic examination of the biopsy sample disclosed vascular fibrous tissue strands and a small area of epithelial denudation in the mucosa (Fig 168) The submucosa showed interlacing strands of reticulum infiltrated with lymphocytes The latter, however, was no greater in degree than that seen in most stomachs examined at necropsy Beneath the area of fibrosis and cellular infiltration the submucosa appeared edematous and the blood vessels seemed dilated The muscle layer was definitely thickened, measuring 0 7 *cm* in the contracted fixed section The muscle fibers themselves appeared entirely normal and there were no signs of inflammation The diagnosis established on the basis of these findings was chronic gastritis with hypertrophy and thickening of the pyloric muscle

From the standpoint of symptoms the patient was unrelieved by the operation The stomach was rechecked on two occasions by x ray the last time on July 9, 1945 (Fig 169) As you can see, there was little change in appearance

acutely or chronically ill The only finding of note on physical examination was sharply circumscribed epigastric tenderness

Laboratory studies were unremarkable save for the persistent presence of occult blood of variable degree in routinely obtained stools Gastric analysis by the fractional Ewald meal method disclosed mild fasting hyperacidity, postprandial hyperacidity (grade one), and definite delay in evacuation of the test meal without overnight retention of food Gastroscopy revealed only mild superficial gastritis involving a goodly portion of the body of the stomach

A representative roentgenogram showing the outstanding finding of the initial roentgen examination on February 2, 1945, is shown in Figure 166 As may be seen, there was a persistent elongated narrowing of the distal



Fig 167 (February 26 1945) Spot roentgenogram of the distal stomach following twenty four days of antispasmodic medication and a stomach rest regimen The appearance is essentially unchanged from that of February 2, 1945

portion of the stomach No other deformity or abnormality was observed in the stomach or duodenum and the stomach was empty of barium within six hours

The patient was placed on a stomach rest program which included tincture of belladonna to the point of tolerance Despite this regimen there was little or no change in symptoms A recheck roentgen study of the upper gastro intestinal tract was made on February 26, 1945 Figure 167 represents a typical roentgenogram exposed during this study It may readily be seen that the stenotic lesion involving the distal stomach was essentially unchanged from that observed twenty four days previously

In view of this, the abdomen was surgically explored on March 14, 1945 Two thoroughly trained, experienced and very skillful surgeons performed

Six years later this man appeared with a return of gastric symptoms of about three months duration This is the film showing a gastrojejunostomy (Fig 171) Please note the narrowing of the entire stomach distal to the gastro-



Fig 170 Pyloric obstruction The appearance of the pylorus in A is somewhat like that of cases under discussion B illustrates high grade twenty four hour retention



Fig 171 Case M G six years later showing extreme narrowing of entire stomach distal to the gastrojejunostomy stoma

jejunostomy suggesting extensive neoplasm or fibrosis Note the circular expansion of the duodenal loop

The patient was subjected to a second operation and a large partial gastrectomy performed This is a photograph of the lesion (Fig 172) He does

of the distal stomach except, perhaps, for slight lessening in degree and extent of narrowing as a result of the pyloroplasty

The patient eventually was separated from military service because of physical disability and I have had no further direct contact with him However, he subsequently came under the care of a gastroenterologist in his home town from whom I receive follow up reports from time to time As of the last report on October 26, 1948, the patient was still troubled by the very same symptoms he had before operation Gastric analysis now is said to show overnight retention of food The roentgen appearance of the pars pylorica has not changed, but there is now evidence of partial obstruction Gastric resection has been advised but the patient has steadfastly refused further surgery



Fig 169 (July 9 1945) Spot roentgenogram showing persistence of narrowing in the pars pylorica The narrowed area seems a little wider and less extensive probably the result of the pyloroplasty

Dr Bockus This problem presented by roentgen evidence of pyloric narrowing is an exceedingly difficult one From the x ray standpoint the differential diagnosis is often impossible I brought over a few slides which illustrate some of our previous experience with lesions of this kind These films (Fig 170) were taken in 1939 This man, M G, presented with a relatively short history suggestive of pyloric obstruction He had a marked hyperacidity The film to the right (Fig 170) is a twenty four hour retention film He was operated upon by Dr Walter E Lee You will note the appearance of the pylorus which is somewhat like the appearance that we have been demonstrating The duodenal cap seems rather well filled Dr Lee in 1939 was unable to demonstrate at operation an actual pyloric lesion He was quite sure that there was no malignancy A gastrojejunostomy was performed

a submucosal carcinoma of the stomach Note the infiltration of the tumor into the thickened pyloric muscle This is a photograph (Fig 175) of the stomach, the film of which was seen in Fig 173, *A* Histologically it proved to be a fibroma in the submucosa of the pylorus It shows beautifully as a milk like tumor between the mucosa and the pyloric muscle I think, Dr Dapena, you will have noticed that in all three of these cases the pyloric muscle itself was markedly thickened

Figure 176 is another instance of carcinoma of the pylorus which gave rise, by roentgen ray, to exactly the same type of pyloric narrowing noted in previous cases

Figure 177 is another instance of pyloric narrowing due to benign pyloric muscle hypertrophy associated with carcinoma of the cardia (not well shown on this slide) Both lesions occurred in the same stomach independent of each other

In summary, the lesson that I wish to leave with you is that in my experience a roentgen defect of the character under discussion must be considered an organic lesion until proved otherwise I do not believe that palpation by the surgeon can be looked upon as ruling out an organic cause for pyloric narrowing sufficient to produce roentgen defects of this type I think that if the patient originally presented were in my family, there would be no hesitation about what would be done She would be reoperated upon without delay I would much rather subject her to an operative mortality risk of 2 per cent and the chance that nothing would be found than I would take the responsibility for delaying operation in order to carry out further diagnostic procedures which could not possibly exclude submucosal neoplasm

(*Question*) Would you be satisfied with a biopsy here?

Dr Bockus I don t think a negative biopsy could be looked upon as being reliable I may say to you that the first case I showed of Dr Lee s if I m not mistaken was biopsied and pronounced negative

This is a bad region We have no truly accurate diagnostic method for differentiating submucosal neoplasm and benign hypertrophy of the pylorus The gastroscope can t do it The examination of the gastric sediment can t always do it If cancer cells are found well and good but if the test is negative, this would not exclude submucosal cancer Certainly the taking of a biopsy of one segment of that long pylorus would not exclude cancer if it proved to be benign

Dr Dapena pointed out in one of our conferences before that under anesthesia something may happen to the pyloric muscle possibly it may smooth out just a little and seem less obvious to the palpating fingers I should like to reiterate that we should not allow these patients to go without operation on the chance that the lesion may be benign pyloric muscle hypertrophy Indeed, in our experience those patients who do have marked hypertrophy of the pyloric muscle will do better with a resection than with any other type of treatment, surgical or medical Any questions?

Dr Dapena I want to ask Dr Berk if he would be satisfied with biopsy in

ing of the pylorus Both Dr Finkelstein and I entertained the possible diagnosis of pyloric muscle hypertrophy in both of these stomachs, indicating at



Fig 176 Carcinoma of the stomach causing a roentgen defect indistinguishable from pyloric muscle hypertrophy



Fig 177 Pyloric muscle hypertrophy in a patient with carcinoma of the cardia

the same time that either one of them could have either a carcinoma or other tumor

Figure 174 is a photograph of the resected stomach shown in Fig 173, *B*,

The Liver

his case which obviously was thickened muscle Isn't it possible that he may have a carcinoma somewhere else

DR BERK My answer is I would not be satisfied I wanted this patient resected at the time of operation I was fortunate to get the biopsy He s no longer under my care

DR BOCKUS Dr Berk, was it you who mentioned a case in which 25 different sections of pyloric tissue were examined before a positive diagnosis of carcinoma was established?

DR BERK As I recall in the case referred to, pyloric carcinoma was diagnosed on the 25th section, they finally found carcinoma cells

DR BOCKUS Dr Dapena, it is my impression that good pathologists occasionally are unable to find carcinoma cells in some instances of slow growing scirrhous carcinoma only to make the diagnosis by finding carcinoma in a regional lymph gland Then reexamination of previous sections of the stomach has resulted in finding a few malignant cells If you haven t had that experience I believe you will have It is because of experiences like this that one hesitates to exclude carcinoma by examination of a biopsy section

EVALUATION OF LIVER BIOPSY IN THE STUDY OF HEPATIC DISEASE

T GRIER MILLER, M D

It is now well recognized that needle biopsy of the liver is a very simple, safe and useful procedure The introduction of a needle into the liver is not particularly new for many decades needles have been introduced for the evacuation of an amebic abscess and as far back as 1895 an Italian by the name of Lucatello introduced a needle with the idea of getting material for microscopic study It is true that he got only some liver cells, but he was able to make smears, stain them and perhaps learn something Then in 1923, two Germans, Bingel and Olivet, revived the procedure It was not until 1939, however that the present method of doing a needle biopsy of the liver was worked out That was accomplished by a Dane named Iverson His technic is the one still in use During that same year Baron in New York employed the method and since that time many workers have done liver biopsy with great freedom Many of you no doubt, are familiar with the publications of McMichael Sherwood and their associates in England Jones and Volwiler in Boston Schiff in Cincinnati, and many others In our own clinic this procedure has been employed for about two years, Dr Edwin Rasberry and more recently Dr Winston K Shorey being the ones who have actually accomplished it

There have been, so far as I know, 15 deaths as a result of liver biopsy I believe all of them occurred several years ago, before the necessity of certain precautions was appreciated I know of but one death in this country and that was in Boston in one of the early cases done by Dr Volwiler The patient had amyloid disease of the liver and the liver tissue was torn when the needle was introduced, the patient bled to death We in about 125 to 150 biopsies have had no serious results and I know of no one who has had any difficulty when reasonable precautions have been taken The procedure should be employed only on patients who are alert and cooperative, and on patients who have a normal prothrombin time The latter is most important, though we have been willing to go ahead in any patient who has a prothrombin over 50 per cent

TECHNIC

The technic is not very complicated The needle that is used is the one modified by Franseen It has sharp biting points and as it is introduced, it is rotated in such fashion that a core of liver tissue is cut out Before the needle is introduced the prothrombin time of the patient s blood, of course,

whether it is in one of the later stages when the fibrosis is marked and other changes have taken place It is, therefore, helpful in prognosis because it aids in determining the exact phase of the disease

In the third place, liver biopsy has been employed with the idea of following the course of the disease By doing repeated biopsies at monthly intervals, for instance, it is possible to determine what kind of progress is taking place whether the liver disease is subsiding, or progressing in an unfavorable way Consequently, it is helpful in the management of liver disease, by indicating whether this or that procedure is worth while

RESULTS

Dr Chester M Jones has recently published a very interesting paper in which he describes serial biopsies on a rather small number, I admit, but a very carefully followed group of patients with cirrhosis of liver By making these serial observations he came to the conclusion, maybe rightly and maybe wrongly (it will have to be confirmed) that the lipotropic substances probably are not very important therapeutically, but the really significant thing in the treatment of cirrhosis of the liver is a high protein diet

Questions have arisen as to the relative value of needle biopsy in comparison with peritoneoscopy and the removal of tissue by that means It is possible, as you know through the peritoneoscope to remove a small section of liver, but necessarily that section must be from the surface of the liver including a part of the capsule Some workers feel that that sort of a specimen does not give as satisfactory information as a specimen that is obtained from deep in the liver substance, the sort of specimen you can get through a needle Dr John G Mateer, for instance, has published a paper in which he makes a comparison of liver material obtained by needle biopsy with other specimens of tissue removed from the surface of the liver by peritoneoscopy I think he probably is a little more inclined to favor the peripheral specimen that can be obtained by the peritoneoscope but certainly that is not the universal opinion

To emphasize the value of the procedure I may refer to the report of Jones and Volwiler, in which they make the statement that among 216 satisfactory specimens (they had done more than that) 79 were essential to a correct diagnosis They don t say that an erroneous diagnosis would have been made otherwise but it would have been a guess In the 79 the diagnosis was definitely established by needle biopsy whereas without it they could not have been sure about the diagnosis I think those figures are significant I have already referred to their 14 cases of Laennec s cirrhosis studied serially, in which they demonstrated the value of the high protein diet

Dr Leon Schiff of Cincinnati has reported on 53 needle biopsies in patients with carcinoma of the liver In 41 of these he was able to make the diagnosis by the needle Furthermore he points out, and we can confirm this, that it is very easy with such a specimen under the microscope to differentiate the various types of carcinoma whether one is dealing with a hepatoma a cholangioma a melanoma or what not

must have been determined and found satisfactory Then the patient must be given some breathing exercises, having him take several deep breaths and then holding his breath until one is sure that he understands how to do that and is able to do it promptly and correctly at the critical time The reason for taking the deep breaths before the procedure is to render the apneic period easier for the patient Also about two hours before the test is performed we are in the habit, and I think it is general practice, of giving the patient a large dose of Synkayvite, a vitamin K preparation, *no matter what the prothrombin* time An hour beforehand we give the patient either codeine or demerol Then the patient is prepared as for any minor surgical procedure

After carefully anesthetizing the skin and the deeper tissues, a nick is made in the skin and the needle, with stilet in place, is introduced through the abdominal or chest wall, whichever is being employed, close to the liver Then the patient takes a few deep breaths, followed by holding his breath While holding his breath the needle is introduced a little farther so that it goes through the capsule of the liver The stilet is removed, the needle is plunged another 2 or 3 to 5 cm and as it is being advanced it is rotated Then a syringe is applied to the end of the needle and suction is made so as to create negative pressure While the negative pressure is maintained the needle is quickly withdrawn The core of tissue in the needle usually slips up into the syringe as the needle emerges Ordinarily a nice, round tubular piece of tissue, perhaps 3 or 4 cm in length and probably about 1 mm in diameter, is thus obtained The whole procedure takes about ten seconds, it takes much longer to describe it than it does to do it

OBJECTIVES

The first objective of this procedure is, of course, to make a diagnosis After all, you appreciate that although we talk freely and glibly about the liver function tests, we often don t know much more about the patient s disease after we re through with these tests than we did beforehand They are helpful perhaps in telling us how well the liver functions in one way or another, but they don't tell us what we d like to know about the actual pathology of the liver On the other hand, by getting this tissue we are sometimes in almost the same position as if we had the liver in our hands, and we are able to make satisfactory microscopic sections Sometimes errors are made, of course, particularly in those patients in whom the liver disease is focal For instance, in carcinoma of the liver it is quite possible to miss one of the malignant nodules, and to get perfectly normal liver tissue But when the disease is diffuse as in hepatitis or cirrhosis one can count on getting material that will lead to a diagnosis in the great majority of cases It is also particularly helpful in differentiating between extrahepatic and intrahepatic obstruction, a condition that sometimes is quite confusing and cannot be absolutely settled by the functional tests

The second objective of needle biopsy of the liver is to determine the phase of the disease One may know that a patient has a cirrhosis but not know whether it is in the early stage without much fibrosis and with much fat, or

Figure 178 shows an area between and including liver lobules in a patient who was in the fourth or fifth month after an attack of viral hepatitis At



Fig 178 Viral hepatitis Section from a needle biopsy specimen of liver in a forty seven year old man The diagnosis had been made four months previously but the clinical manifestations had disappeared The section shows infiltration of the portal areas with inflammatory cells



Fig 179 Cirrhosis of the liver The subject was a forty five year old chronic alcoholic The section shows the connective tissue to be greatly increased and to contain proliferating bile ducts The parenchymal cells contain large quantities of fat

the present time he is free of jaundice, and it will be very interesting, after a year and since he has lost his jaundice and his functional tests are nega

Other workers, Topp and Lindert, have reported on 6 cases of hemochromatosis in which the diagnosis was easily made, and I will show you a slide on one of our cases in which also it was quite easy to make that diagnosis

Now just a word about our own experience Taking 120 biopsies that we've done, or that my associates have done (and this is not quite their complete series), there were 5 failures That is not a large error, about 4 per cent, and, after all, remember that my associates were completely inexperienced in the beginning, and that today they are doing a far better job than they did in the first 50 cases Of the 120, 29 patients had cirrhosis and in 25 of those there was no question whatever about the diagnosis on the basis of the histologic study, *in 4, there was some question but eventually it turned out that* they too were cirrhotic There were 17 patients who had viral hepatitis, and in all but one of those cases there was no question whatever about the diagnosis on the basis of the histologic specimen, independent of any clinical or other laboratory observations I think that the diagnosis had been suspected on a clinical basis in all those cases and yet it was a great satisfaction to look into the microscope and actually see the changes that had occurred

We have had 13 patients with malignant disease, 9 of these had carcinoma, 3 had sarcoma, and 1 had a melanoma We had 8 patients in whom a diagnosis of pericholangitis was made I say pericholangitis rather than biliary cirrhosis of the liver because it is a somewhat more inclusive term, it includes perhaps some patients who had primarily obstruction to the biliary ducts on the basis of some extrahepatic disease We had 2 patients with tuberculosis, there was a little question about one of them, a question by the pathologist, but no question whatever about the diagnosis in the other patient We had 2 patients with hemochromatosis Unfortunately, in another recently observed patient I was fearful to have a biopsy although I suspected he had hemochromatosis He had diabetes and he had a questionable discoloration of the skin I had a skin biopsy—it was negative We studied his urine for melanin and that was negative We knew he had gallstones and so I finally decided that it was justifiable to operate on him and, incidentally, while doing that, to get the biopsy At operation a large mass of deeply stained glands was encountered under the liver, a biopsy was taken from that mass of glands, but the pathologist on that basis couldn t make a diagnosis We then took a liver biopsy and removed his gallbladder When the specimens from the liver were studied there was no question whatever about his having hemochromatosis, and since that time he has developed other disturbances confirming the diagnosis We could easily have made that diagnosis by introducing a needle into his liver and so we could have saved him the operation

We had one patient, a child, with glycogen disease of the liver

In 40 cases, the liver tissue was reported as normal Those were patients in whom there was some suspicion about liver disease but we weren t sure These cases have not been analyzed as yet, and I don't know how helpful it was to have the biopsies in those particular cases I can see that it might have been very significant and I know that Dr Shorey is now in the process of studying those cases

Figure 179 shows a slide from a patient who had Laennec s cirrhosis, the alcoholic type of cirrhosis You see the very marked fatty infiltration throughout the liver lobule You will also notice the strands of fibrous tissue between the lobules

In Fig 180 the patient had carcinoma of the liver This is Dr Magee s patient I don t know what he thought, but we thought when we saw the patient that he had a cirrhosis of the liver There wasn t much question about it on the basis of all the tests we could make We finally did this needle biopsy and to our surprise here is a vein completely filled with malignant cells There are also scattered malignant cells throughout the liver

The final slide (Fig 181) shows a certain amount of iron pigment, the diagnosis being hemochromatosis

AN EVALUATION OF HEPATOSPLENOGRAPHY

HENRY J TUMEN, M D

The search for means of diagnosing with accuracy what goes on in the liver has of course, not been completely successful and the fact that we use so many different diagnostic procedures indicates that none is entirely satisfactory A number of years ago the idea was suggested that if we could visualize the liver roentgenologically, we might be able to determine more about its diseases and, particularly, to determine the presence in the liver of what can be called space taking lesions, lesions that make their presence known by destroying or pushing aside the normal liver tissue

With this idea in mind it was suggested that the liver be visualized by the administration of substances which would take up their residence in the liver and cast shadows on x ray films The substance which has been most widely used for this is thorotrast, which is a solution of thorium dioxide Thorium being one of the heaviest of the metals, casts an x ray shadow The principle involved is simply this—that shortly after its administration it is taken up by the reticuloendothelial cells Since those cells are present prominently and extensively in the liver and spleen these organs become radio-opaque and can be visualized satisfactorily

TECHNIC

The technic of this procedure is extremely simple The preparation is available commercially under the name of Thorotrast and is usually marketed in 25 cc ampules The ordinary dose is either 50 to 75 cc, in other words, two or three ampules We have usually found two ampules to be adequate The material is given slowly intravenously Occasionally there is a transient vasomotor reaction but this usually does not occur if the thorotrast is given reasonably slowly Within a very short time a half hour or three-quarters of

tive, to have another specimen to compare with this one I think there's nothing to point out here except the marked infiltration with chronic inflam



Fig 180 Metastatic carcinoma The section is from the liver of a sixty three year old man and shows infiltration of the liver parenchyma by metastatic malignancy

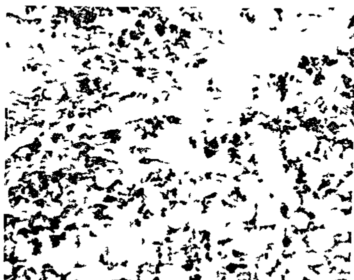


Fig 181 Hemochromatosis The section is from the liver of a forty seven year old woman in coma and shows a great amount of iron pigment in the liver cells The pigment is demonstrated by a *special iron stain*

matory cells all through the interlobular area and even out in the liver lobules to a certain extent Also, a few, poorly formed, small bile ducts are demonstrable

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an hour, in fact by the time that the thorotrast has been given, there usually is a sufficient amount in the liver to enable it to be visualized The original technic called for the giving of three ampules on three successive days, but that usually has not been necessary If 50 or even 75 cc of thorotrast is put *into 500 cc of saline and given very slowly* intravenously, the total amount can be given at one time

DIAGNOSTIC RESULTS

When thorotrast was originally introduced, it was thought that it would have very widespread diagnostic use It was hoped that it would be valuable in determining whether a mass felt in the abdomen was really the liver or the spleen and in the differential diagnosis of diseases like *cirrhosis*, since in



Fig 182 Thorotrast visualization of normal liver and spleen Note the uniform density of the organs

cirrhosis there is usually a lessening of the total bulk of functioning liver tissue and of the reticuloendothelial cells, so that the shadow cast would be less dense For these purposes, however, thorotrast has largely been shown to be unnecessary or inadequate The chief purpose for the use of thorotrast has come to be the recognition of disease conditions like metastatic or primary carcinoma, or abscesses of the liver, which destroy liver tissue Our own experience has largely been in the field of attempted recognition of carcinoma of the liver and it is about that that I wish chiefly to speak

There is no doubt that thorotrast does give some very definite roentgen assistance in deciding various things about the liver This can be shown best by pointing out some of the illustrations that we have and then we will refer to the general principles later

Figure 182 indicates a normal liver It is possible to see a very uniform



Fig 183 Thorotrast visualization of normal liver and spleen The linear markings in the liver probably represent vascular or biliary channels

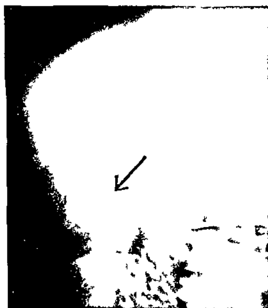


Fig 184 Thorotrast visualization of liver suggesting metastatic carcinoma Note radiolucent area in body of liver

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Fig 187



Fig 188

Fig 187 Thorotrast visualization of a large primary carcinoma involving lower border of the liver

Fig 188 Thorotrast visualization of liver demonstrating mottling resulting from extensive metastatic carcinoma



Fig 189 Visualization of liver at post mortem demonstrating changes due to extensive carcinoma (Same liver as in Fig 188)

shadow The fact that there are smooth and unbroken shadows of both the liver and the spleen is characteristic of organs in which there is no roentgen evidence of either carcinoma or abscess

Figure 183 also is the x ray of a normal individual, or at least of an individual whose liver is normal The liver has a relatively smooth and uniform appearance

In Fig 184 we see a liver in which the presence of metastatic disease is suggested by this somewhat radiolucent shadow in the central portion of the liver I might point out the various channel markings which are presumably vascular or biliary, but the exact significance of which isn t known It s particularly these translucent appearances that are outstanding in this section of the liver And again in Fig 185 is a liver in which, although not seen too dis

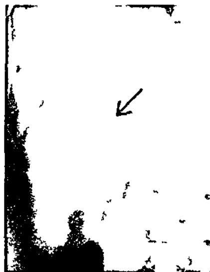


Fig 185



Fig 186

Fig 185 Thorotrast visualization of liver demonstrating translucent areas indicative of metastatic carcinoma

Fig 186 Thorotrast visualization of liver demonstrating translucent areas indicating presence of metastatic carcinoma

tinctly, various translucent shadows appear Figure 186 is the liver of an individual in whom carcinoma was present and in which these translucencies are noted

The individual in Fig 187 had a large primary carcinoma of the liver which involved the lowermost portion and caused this large concave translucency here, taking out the lower portion of the liver edge

Figures 188 and 189 present an extremely striking example, which unfortunately is shown much more vividly in the postmortem specimen than in the film taken during life You can see a very marked suggestion of destruction or infiltration and invasion of the liver tissue along the border This was forty-eight hours after 50 cc of thorotrast was given At post mortem when the liver was taken out and x rayed, the pathologic basis for the shadows

trast and in which one can see very distinctly the fact that her liver is still visualized quite well and her spleen also for that matter, so that there is every evidence that thorotrast has remained in this patient, casting this shadow of the liver, over these many years

It is that particular fact that has rendered the use of thorotrast a little questionable and which should be really the chief thing about which we have to talk, because there can be no doubt that in many of the patients in whom thorotrast has been used it has been of tremendous diagnostic value The rate of excretion or elimination of the thorotrast from the body is extremely slow and, as a matter of fact, it is hardly likely that it ever disappears to any great extent from the body once it is given Then, of course, there is the fact that thorium is a radioactive substance, that it has a very long life of radioactivity and that, in addition to the thorium itself, the products of its degeneration are extremely potent When thorium breaks down in the body it forms substances like mesothorium and radiothorium and thorium emanation that have a definite degree of radioactivity The gamma radiation activity of the amount of thorium that we use has been compared to that of from 1 5 to 3 micrograms of radium and the same amount of alpha radiation is also supposed to be emanated from this amount of thorium

In animal experiments it has been shown that the administration of thorium in the amount that we use has certain dangers It has been possible to produce in animals various sarcomas and carcinomas of bone for instance by the injection of thorotrast directly into the bone marrow It has been possible to produce various tumors some of which are carcinomatous, in animal experimentation, and there is some possibility that thorium has caused cirrhosis to develop in animals to which it has been given The experimental evidence, therefore is that thorium can produce toxic damage of serious types Other evidence indicates quite definitely that under certain circumstances of prolonged administration or long exposure to thorium, changes in the hematopoietic system have been produced and various types of anemias have been caused in the experimental animal

When we turn to the human evidence we find, of course the counterpart of these effects in patients who have been exposed to radium A few years ago there was an epidemic of radium poisoning in individuals who had been employed in industries in which they had been exposed to or ingested small amounts of radium over long periods of time Many of these individuals developed aplastic anemias or other severe disturbances of the bone marrow and many of them developed various types of carcinoma particularly bone tumors The interesting thing that was brought out in the study of these patients was the very long latent period that was involved—the fact that many of these patients didn t develop these terrible consequences of radium poisoning until ten or fifteen years had elapsed—and it is that long latent period that has us worried The fact remains that in the animal experimentation that has been done the latent period between the giving of the thorotrast and the development of the disease consequences has corresponded to about ten or fifteen years in the lifespan of a human being

obtained during life was indicated in the mottled appearance and the suggestion of destruction and pushing aside of a tremendous amount of the liver tissue

Figure 190 shows something else that we think advisable to speak about This is the fact that the administration of thorotrast to a patient who has been suspected of having malignancy, or who has had some abdominal malignancy and in whom the possibility of metastatic carcinoma of the liver is feared, may at the beginning of the study show rather equivocal findings which become much more distinct as time goes on This is a patient who had carcinoma of the stomach and who was seen sometime later with questionable evidence of metastasis The original thorotrast films taken twenty four hours after the administration of thorotrast are definitely suggestive but when we

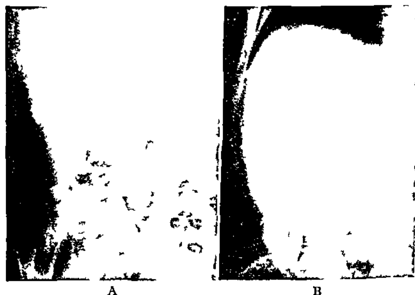


Fig 190 Thorotrast visualization of liver Films taken twenty four hours (A) and eight months (B) after administration of thorotrast Note the increased mottling of the liver in (B), indicating the growth of metastatic carcinoma in this period of time

look at the film taken eight months later the patient having survived that period of time, one can see the amount of destruction that has gone on in the liver during that period of time

PROBLEMS IN USE OF THOROTRAST

The diagnostic value of thorotrast in the demonstration of these definite metastatic processes therefore seems to be fairly well established, and yet there are very definite reasons why this particular method of study has not come into popular use and is not considered to be in very good repute The chief reason is, of course that when thorotrast is given it is fairly permanent and remains in the liver for an indefinite period of time We have one film which was taken approximately seven years after the patient was given thoro-

who have been given thorotrast and who have survived to determine just how safe it is I have now two patients who were given thorotrast three and five years ago who apparently are quite well and happy and with no ill consequences, but I certainly would prefer to wait much longer before saying that thorotrast is altogether safe

Finally we sincerely hope that there will soon become available various substances possibly iodine compounds, which can be given and which will visualize the liver but which will be very rapidly excreted from the body and disappear before they can cause ill effects These various considerations, therefore, lead me to the conclusion that the administration of thorotrast should not be a routine procedure, but that the substance should be used when there is great need for the assistance it gives and with full realization that its dangers are not fully known

EPIDEMIOLOGIC AND CLINICAL FEATURES OF VIRUS HEPATITIS

W PAUL HAVENS, JR, M D

INTRODUCTION

Two apparently closely related forms of viral hepatitis are now recognized (a) infectious hepatitis (catarrhal jaundice epidemic hepatitis) and (b) homologous serum hepatitis (yellow fever vaccine jaundice syringe jaundice) The first term is used to indicate the naturally occurring disease The second term, homologous serum hepatitis is an artificial one created to designate that form of disease produced by the parenteral inoculation of blood or its products accidentally contaminated by a virus of hepatitis [1] Clinically and pathologically, these two forms of hepatitis are indistinguishable after onset of disease They are believed to be caused by viruses which have certain similar properties in that they are filtrable capable of considerable resistance to heat and up to the present have apparently not been transmitted to any of the common laboratory animals

Two exceptions in the clinical identity of these two forms of hepatitis are concerned with the type of onset and the length of incubation period In the epidemic disease, the onset is frequently abrupt occurring after a relatively short incubation period of fifteen to forty days in contrast to the vague, insidious onset of homologous serum hepatitis which occurs from sixty to one hundred and twenty days after the reception of parenterally introduced hepatitis virus In addition to these differences are certain others which are related to distribution of virus in the body method of transmission of disease, and absence of cross immunity [2,3] In patients with the epidemic disease virus is present in the stool and in the blood in the acute phase Up to the present patients with homologous serum hepatitis have not been found to

We still have to say, therefore, that there are certain unknown features about the administration of thorium that remain to be evaluated From a human standpoint it is true that the clinical evidence to date has not demon strated a large number of serious consequences The work on thorotrast in this country was done very largely by Dr Yater His reports seem to indicate that patients who've been followed for as long as ten years after the adminis tration of thorium have not shown any ill effects I had a letter from Dr Yater recently in which he reiterated that statement Yet, there are reported in the literature occasional patients in whom something like aplastic anemia has developed nine, ten or twelve years after thorium has been given The number of cases is too small to be considered conclusive or definite evidence and the evidence is purely circumstantial but, nevertheless, it's there

I have a patient at the present time, a woman who had thorium given to her a number of years ago, who now has a very bizarre type of anemia which defies the attempts of the hematologist as to a definite classification, but whose bone marrow shows an extremely abnormal function In her case the possi bility of thorium poisoning has been raised It is only fair to state we are still a little fearful of the use of thorium

VALUE OF THOROTRAST

One question we can ask ourselves is, how valuable is thorium in the picking up of the earliest stages of malignancy? In other words, how valuable is thorium at a time when it is most needed diagnostically? Up to the present time, we've used thorium in 20 patients With one exception, all of these had carcinomas of various types Of the 19 patients who had carcinoma, it is very probable that the thorium was not a definite diagnostic factor in 12 Palpation of the liver, determination of liver dysfunction by the bromsulfalein test or the demonstration of an increased alkaline phosphatase or, very probably, the doing of a liver biopsy as Dr Miller has just discussed, would have diagnosed the presence of carcinoma without the administration of thorotrast

In some of the other patients, and one of those was shown here, the admin istration of thorotrast did not immediately demonstrate the presence of carcinoma In other words, there was a stage in the development of carcinoma when the thorium was not of particular value It didn't show the presence of carcinoma until the lesion had progressed to a stage at which it might have been picked up by other diagnostic procedures Therefore, at the present time, I am not prepared to say that this method, with its latent dangers, is one that presents us with sufficient assured diagnostic assistance to make it altogether wise to use I believe that it is probably best to limit the use of thorotrast to individuals in whom the presence of carcinoma is fairly well established so that the likelihood of prolonged life span isn t very great, or to limit its use to individuals who have reached an age level at which ten or fifteen years will probably carry them pretty much to their expected life span anyhow, so that the consequences of the thorium administration might not be so serious

I feel, myself, that it will take a number of years of studying of the patients

patients developing permanent residual hepatic disease is, as yet, undetermined, although accumulating evidence suggests that it is small In a well-controlled study made by Kunkel and his associates[4] in New York, only 2 3 per cent of 350 young men with hepatitis had any signs of residual disease at the end of a year It is evident that the results of careful observations of large numbers of patients by means of follow up studies, biopsy of the liver and tests of hepatic function will be necessary to determine just how large this group will eventually be

Of interest in this regard are recent reports from Denmark[5,6] of chronic hepatitis in older women after the menopause The onset of disease in such patients was usually vague and insidious, with anorexia and malaise and the subsequent appearance of jaundice In many patients, clinical improvement was apparent after four or five months, jaundice diminished gradually, appetite returned and gain in weight occurred However, it was common for such patients to have what appeared to be relapse in eight or nine months after the onset with return of jaundice Ascites frequently appeared, and death occurred in as many as 50 per cent of some groups of patients The histologic findings in the livers of such patients were consistent with the diagnosis of subacute yellow atrophy of the liver

DIAGNOSIS

Early in the disease, in the pre icteric phase anorexia, nausea and epi gastric distress direct attention to the gastrointestinal tract Posterior cervical adenopathy has been described as occurring frequently in this disease Evidence of dysfunction of the liver may be indicated quite early and the bromsulfalein dye retention test is usually the first to become abnormal, often indicating hepatic injury as early as the second to the third day of fever The cephalin cholesterol flocculation and the thymol turbidity tests become positive in the next few days, and of great importance is the appearance of bilirubin in the urine at the end of the first week of disease, often before clinical jaundice is apparent

During the febrile pre icteric phase the differential diagnosis is often dependent on the geographic location The diseases ordinarily considered are *bacillary dysentery, typhoid paratyphoid fever, malaria, sandfly fever* and *dengue* The subsequent course of disease and the demonstration of specific causative agents or their antibodies aid in making the distinction Infectious mononucleosis often constitutes a problem in differential diagnosis

A large percentage of the lymphocytes found in the peripheral blood of patients in the pre icteric phase of infectious hepatitis are characterized by heavy basophilic cytoplasm containing vacuoles and eosinophilic granules with large blocks of chromatin in the nucleus It is impossible to distinguish this type of cell from the cell usually considered to be pathognomonic of infectious mononucleosis illustrating the difficulty of differential diagnosis particularly in the pre icteric phase when posterior cervical adenopathy may be present The difficulty is enhanced by evidence of hepatic dysfunction in a large proportion of patients with mononucleosis with jaundice occurring in

have virus in the stool although it is present in the blood during the acute phase and at various periods during the prolonged incubation period, constituting a hazard in utilizing pooled plasma from donors who appear to be well Infectious hepatitis may be produced experimentally by either parenteral or oral inoculation of volunteers, but there is good reason to believe that naturally the disease is transmitted by the oral route In contrast, homologous serum hepatitis has not been transmitted by the oral route with two possible exceptions, and it is believed to be an artificially induced disease in practically all instances Lastly, cross immunity apparently does not exist between these two diseases, since patients convalescent from one form of hepatitis are susceptible when exposed to the other

CLINICAL COURSE OF INFECTIOUS HEPATITIS

The disease may be divided into two phases—pre-icteric and icteric—although an undetermined number of patients have hepatitis without jaundice Anorexia, nausea, vomiting and tenderness in the epigastrium appear early in the pre icteric phase, and frequently pressure on the epigastrium causes a sense of nausea Infectious hepatitis is frequently initiated by chill or chilly sensations, with malaise, headache, prostration and generalized aches and pains The temperature may be elevated as high as 102 F or even 104° F , and declines gradually over a period of five to seven days by lysis to normal Bilirubinuria occurs late in the pre icteric phase, and leukopenia is characteristic in this period, with an early decline in lymphocytes followed by a decline in polymorphonuclear leukocytes At the end of the first week of disease, atypical lymphocytes similar to those usually considered pathognomonic of infectious mononucleosis make their appearance

The icteric phase usually begins at the end of the first week of disease At this point, many patients experience a sense of well being for one or two days, and then anorexia, nausea and vomiting reappear The liver usually becomes palpable and tender, and the spleen is enlarged in a small percentage of patients Jaundice increases, reaching a peak in two weeks, after which it begins to wane, disappearing in most patients at the end of the fourth or fifth week of disease The liver usually is no longer palpable after that time, and splenomegaly disappears The nausea, vomiting and epigastric tenderness are most evident at about the time when jaundice reaches its maximum intensity In many patients, a dramatic clinical change occurs at that point, with a return of sense of well-being and appetite

The available evidence suggests that infectious hepatitis is in general, a benign and self limited disease The mortality rate is extremely low—less than 4 per 1000—although the morbidity may be quite high in various outbreaks Complications are unusual and include pneumonia and rare neurologic disorders such as transverse myelitis and lymphocytic meningitis Relapse, however, is not uncommon, and it is not unusual for patients to have an apparently uneventful recovery followed by recurrence of symptoms, with malaise, anorexia, abdominal discomfort and jaundice Recovery from relapse is usually complete, although chronic hepatitis may develop The exact percentage of

disease is in the feces and may be transmitted by the intestinal-oral route, and, as far as is known, the virus of serum jaundice is in the blood only and is transmitted by parenteral inoculation The following discussion relates to the naturally occurring disease, since the other is arbitrarily classified as one transmitted artificially by man

GEOGRAPHIC DISTRIBUTION

Infectious hepatitis apparently occurs throughout the world, reports from widely separated areas including the United States, Scandinavia, North Africa and the South Pacific Islands attest its generalized distribution Certain areas have a record of high incidence, such as the countries surrounding the Mediterranean Sea

SEASON

A seasonal prevalence has been noticed in many parts of the world, with an increase in incidence during the late fall and winter months, declining during the late spring and summer However, the disease may occur at any time and in Chile it has been pointed out that the incidence is relatively stable throughout the twelve months of the year Of interest in this regard is the pattern of incidence of disease in Germany during the years from 1944 to the present In 1945 there occurred a sharp outbreak of disease in the winter, declining in the spring Since that time up to the present, there has been slight seasonal fluctuation The reason for the fairly steady regular occurrence of disease in contrast to the characteristic sharp seasonal fluctuation is undetermined, although it has been suggested that the occurrence of the artificially transmitted disease in which seasonal factors would not influence the time of appearance, may account for the change in pattern of incidence [3]

AGE

Infectious hepatitis is primarily a disease of childhood, although young adults up to thirty are highly susceptible if they are placed in an area where there is sufficient virus, and live under conditions of sanitation wherein the transfer of virus is facilitated

EPIDEMICS

Epidemics may be explosive rising to a sudden peak, but more frequently they tend to develop slowly, gaining impetus over a period of one to two months It has been suggested that such a pattern is that of a disease which has a long incubation period of twenty to forty days and in which the spread is apparently related to personal contact In family outbreaks, the first case is frequently followed in twenty to thirty days by 2 or 3 other cases Among troops it was observed that when large groups went into areas where infectious hepatitis was endemic, explosive outbreaks occurred suggesting that a large number of men had been infected simultaneously The bulk of evidence at the present time suggests that variations in strain, pathogenicity and infec

a smaller percentage of cases Of importance may be the heterophile antibody determination which becomes elevated in a goodly percentage of patients with mononucleosis while it rarely rises higher than a titer of 1 56 in infectious hepatitis In the latter disease, the heterophile antibody is absorbable on boiled guinea pig kidney

The differential diagnosis from acute infections of the upper respiratory tract may often be difficult in the pre icteric phase because a certain proportion of patients with hepatitis have an onset with coryza, cough and sore throat The percentage of patients with these symptoms varies in different outbreaks Lastly, the nausea, vomiting and abdominal pain with slight fever often are suggestive of acute appendicitis, and many patients with infectious hepatitis have appendectomy performed only to have jaundice occur a few days postoperatively The normal or low leukocyte count and the absence of localized tenderness in the right lower quadrant are highly suggestive, however, of the diagnosis of hepatitis

When jaundice appears, the differential diagnosis may be concerned with acute or subacute cholangitis in which the leukocytosis and the recurrent chills and fever may be of assistance Weil s disease may be considered, but the leukocytosis, the severe muscular pains and conjunctival hemorrhages, as well as the demonstration of the causative organism or antibodies to it, are of assistance Yellow fever must also be considered as a remote possibility, depending on the geographic location

Jaundice may also develop in a number of acute and chronic infectious diseases, as in malaria, brucellosis, amebiasis, occasionally in pneumococcic pneumonia, general septicemias and syphilis and, as mentioned before, not infrequently in infectious mononucleosis

In addition to the jaundice associated with various infections, one also has to consider other types, including hemolytic forms, hepatocellular forms resulting from the toxicity of chemicals, notably the halogenated hydrocarbons, and, finally, obstructive jaundice due to extra- or intrahepatic obstruction of the biliary tract by calculus or neoplasm

The differential diagnosis of jaundice is increasingly difficult in older patients, and this is particularly true at the present time when the occurrence of homologous serum hepatitis following the reception of transfusions of plasma or whole blood is apparently increasing A careful evaluation of the history, physical examination and certain tests of hepatic function are necessary, and even with all the information available from such observations the final diagnosis, particularly in older patients, must occasionally be made by biopsy of the liver or by exploratory laparotomy

EPIDEMIOLOGY

It is of interest that although these two forms of viral hepatitis, the epidemic disease and the artificially transmitted disease, are clinically similar and pathologically indistinguishable, their epidemiology apparently has revealed certain distinctions which may be conditioned by previously described differences in behavior of their causative agents Thus, the virus of the epidemic form of

disease is in the feces and may be transmitted by the intestinal-oral route, and, as far as is known, the virus of serum jaundice is in the blood only and is transmitted by parenteral inoculation The following discussion relates to the naturally occurring disease, since the other is arbitrarily classified as one transmitted artificially by man

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tivity of virus, in addition to certain environmental factors such as crowding and poor sanitation in areas where the disease is endemic, are important in conditioning the exact pattern of spread of disease [7,8]

TRANSMISSION OF DISEASE

The exact way or ways in which infectious hepatitis spreads are not determined It is known that one can produce this disease experimentally by feeding infected material, suggesting that this may be one of the important ways of transmission In outbreaks in institutions for feeble-minded, the highest rate of attack is in the group of lowest intelligence in which good sanitation is most difficult to maintain, suggesting once again that personal contact and the intestinal-oral route may be of importance in spread of disease A number of water borne outbreaks, as well as food- and milk borne outbreaks, have been described, although there is not sufficient evidence to indicate that these are the most common manners of transmission

Attention has been called repeatedly to the respiratory route as a possible way of spread The fact that a goodly percentage of patients in certain outbreaks begin their disease with symptoms related to the upper respiratory tract has supported this concept, although there is insufficient experimental evidence at present to sustain it

The possibility of transmission by insects has been considered, both mechanically or by biting, and, lastly, the possibility of the artificial transmission of infectious hepatitis is important The presence of hepatitis virus in the blood of patients, its high degree of resistance to ordinary procedures of cleansing, and its infectivity by parenteral inoculation suggest the possibility that it may be transmitted accidentally more often than is recognized

IMMUNITY

Epidemiologic evidence is supported by a limited amount of experimental data which suggest that a degree of immunity follows an attack of infectious hepatitis Volunteers who have contracted the disease experimentally were immune when attempts to reinfect them were made In addition, the fact that normal human gamma globulin prevents the disease suggests that the normal human population has been exposed during its years of maturation to hepatitis virus and has developed a degree of immunity This is in accord with the fact that infectious hepatitis is a disease of childhood primarily and, although young adults are susceptible under proper conditions, the incidence of disease declines rapidly after thirty years of age [3]

SUMMARY

As a result of investigations of recent years a better concept of the natural history of infectious hepatitis has been established, certain aspects of the clinical course have been more clearly defined, and the actual pathogenesis of the disease is now more widely appreciated This disease has been classified as one of viral etiology which may be spread by the intestinal-oral route and may be prevented by passive immunization with gamma globulin Epidemio

logic and experimental data suggest that two forms of viral hepatitis exist, and that the form commonly known as homologous serum hepatitis is one apparently created by man insofar as it has to do with the artificial transmission by contaminated products of human blood or syringes The exact relationship between these two types of disease is not known, although the demonstration of certain differences between them suggests that, although they may be closely related, they are not identical diseases

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EVALUATION OF FLOCCULATION TESTS IN HEPATIC DISEASE

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During recent years a number of tests which apparently depend, at least in part, on qualitative and or quantitative changes in the serum proteins have been developed and used as aids in the study of diseases of the liver and biliary tract Although not strictly accurate, the use of the term ' flocculation tests is convenient for reference to these tests as a group As the cephalin cholesterol flocculation test of Hanger[1] and the thymol test of Maclagan [3] probably are the most widely used tests of the group at present they will be the subject of most of this discussion The recently developed zinc sulfate turbidity test of Kunkel [4] on the basis of preliminary observations, also offers promise of being a valuable addition to this group of tests The Maclagan modification of the serum colloidal gold test[5] has been used extensively by some laboratories The Ducci modification of the serum colloidal red reaction[6] appears to yield results that are almost identical with those of the colloidal gold test and has many technical advantages over the latter It therefore

appears to be preferable if one of these two tests is to be used There is some question, however, as to whether either of these two tests adds sufficient to the information gained from the joint use of the cephalin and thymol tests to warrant their *routine* use Their principal value thus would appear to be the provision of confirmatory information when the results of the other flocculation tests' are equivocal

MECHANISMS OF THE 'FLOCCULATION TESTS

A frequently asked question is ' Which one of the flocculation tests is best for routine use? The information obtained with any one test depends on (1) the nature and stage of the process being studied, and (2) whether the test is being used to detect liver disturbance or to aid in the differential diagnosis of jaundice As the clinical value of the individual "flocculation test varies with these factors and the underlying mechanisms of the various tests are not identical, no *single* test is adequate for "routine use The proper interpretation of these tests depends, to a large extent on the familiarity of the observer with the factors influencing their responses An understanding of the underlying mechanisms, therefore, is essential Unfortunately, the mechanisms are not entirely clear, but sufficient information is available to indicate that the factors governing the responses of the various tests mentioned above are not identical Although the factors required for the development of a positive response with each of these tests all may be present at the same time, frequently they are not, and their simultaneous presence or absence may have certain clinical significance This constitutes an additional reason for the use of certain of these tests as a group in the routine study of hepatic and biliary tract disease

Some of the factors involved in the mechanism of the *cephalin cholesterol flocculation* test are apparent from the following summary of the experimental observations of various investigators [7, 8]

C C Reagent plus normal human serum	No Flocculation
C C Reagent plus normal human albumin	
C C Reagent plus normal human albumin plus normal human gamma globulin	
C C. Reagent plus normal human gamma globulin	Flocculation
C C Reagent plus normal human gamma globulin plus abnormal albumin	
C C Reagent plus abnormal gamma globulin plus normal albumin	
C C Reagent plus abnormal gamma globulin plus abnormal albumin	
Hypersensitive C C Reagent plus normal serum	

It is obvious, therefore, that the response of this test may be influenced by a number of factors, all of which must be taken into consideration in the interpretation of the results obtained

In our laboratory, the use of the *thymol flocculation test* has proved to be of value as a supplement to the thymol turbidity test Thymol flocculation possibly may require the presence of some factor in addition to those required for the production of increased thymol turbidity Whether or not this proves

to be the case, the presence of a positive thymol flocculation test leaves no doubt concerning the significance of a borderline turbidity reading, whereas a negative thymol flocculation test raises a question concerning the significance in respect to hepatic disturbance of a slightly elevated thymol turbidity reading Some of the factors involved in the response of the thymol test two of which are not yet clearly defined are as follows [8, 10, 11]

Thymol Reagent plus normal serum	No Turb * No Floc
Thymol Reagent plus abnormal serum	Turb and Floc Turb No Floc Floc No Turb No Floc No Turb
Thymol Reagent plus extracted positive serum†	No Turb No Floc
Thymol Reagent plus extracted positive serum plus lipid	Turb and/or Floc
Thymol Reagent plus normal or abnormal gamma globulin	No Turb No Floc
Thymol Reagent plus normal or abnormal albumin	No Turb No Floc
Thymol Reagent plus normal gamma globulin plus lipid	No Turb No Floc
Thymol Reagent plus abnormal globulin ‡	No Turb No Floc
Thymol Reagent plus abnormal globulin plus lipid	Turb No Floc ?
Thymol Reagent plus abnormal globulin plus hepatitis type gamma globulin plus lipid	Turb and Floc ?
Thymol Reagent plus positive serum plus human serum albumin (excess)	No Turb No Floc

It is of some clinical importance to recognize the fact that the administration to patients of human serum albumin may, through its inhibitory action, convert positive cephalin cholesterol flocculation and thymol responses to negative or less positive responses and thereby may falsely suggest an improvement [11]

According to Kunkel [4] the zinc sulfate turbidity test provides an estimate of the amount of gamma globulin present in the serum Thus it will be influenced by many processes other than liver disease However, when other processes can be excluded, it appears to be of value in suggesting the presence of hepatic disease, in following the course of established hepatic disease and as an aid in the differential diagnosis of jaundice (positive responses apparently are uncommon in extrahepatic obstructive jaundice) It seems doubtful if this test will supplant either the cephalin cholesterol or thymol tests in the study of hepatic and biliary tract disease, as the mechanisms differ and the latter two tests may prove to be more sensitive or specific for certain types of hepatic disturbance However as stated previously, this test may be a valuable addition to these two tests for the routine study of hepatic and biliary tract disease

The *colloidal gold* and *colloidal red* tests[5, 6, 12] also are thought to depend

* No turb refers to normal turbidity Turb refers to greater than normal turbidity Floc' refers to flocculation

† Extracted positive serum—ether extraction in cold to remove lipids of serum yielding positive thymol reaction

‡ Abnormal globulin —exact identity obscure Recant et al suggest is globulin other than gamma globulin Cohen et al suggest is a beta globulin Kunkel et al suggest both beta and gamma globulin may be concerned

primarily on changes in the gamma globulin fraction of the serum Positive responses have been obtained when quantitative increases in this fraction have not been measurable or, at least, well defined Thus qualitative changes in this fraction probably are concerned The possibility that factors other than gamma globulin may influence the response also remains

TECHNICS

Interpretation of the responses of these tests requires a knowledge of the technics employed Many technical factors are capable of influencing the results of the cephalin cholesterol flocculation test[13] and I am reluctant to accept results obtained by laboratories that perform this test only sporadically

An unfortunate situation exists in respect to the thymol test in the present lack of an uniformly accepted standard for photoelectric estimation of turbidity The normal range of values will vary with the standard and method of calibration employed by the laboratory concerned Thus thymol turbidity readings obtained with the method of calibration and standards used in our laboratory[3] are only about half those obtained when the Shank and Hoagland method of calibration and standards[14] are used It is hoped that it will soon be possible to stimulate the adoption of one method of calibration by all laboratories on the basis of study and recommendations made by an authoritative advisory group such as the Subcommittee on Liver Diseases of the National Research Council or the Subcommittee for Standardization of Laboratory Methods Used in Gastroenterology recently organized by the American Gastroenterological Association

Thymol turbidity readings also vary with the pH of the thymol solution that is employed Thymol solutions at two different pH values are being employed, that originally recommended by Maclagan being pH 7 8, and one at pH 7 55 being employed by Mateer and his associates [15] One commercial concern recently has made available a thymol buffer adjusted to still another pH, namely 7 65 Recent studies in our laboratory indicate no special advantage of one pH over the other, the range of normal response varying however, with the buffer used Thus, although the pH 7 55 buffer usually gives somewhat higher results, the upper limit of normal is also somewhat higher We, therefore, continue to use the pH recommended by Maclagan Mateer and his coworkers, however, feel that the more positive responses are obtained with the pH 7 55 buffer Recent studies of this question at the U S Army Hepatitis Center in Germany, carried out under the Commission on Virus and Rickettsial Diseases, tend to support the findings of Mateer and his associates In viral hepatitis, at least, more positive responses were obtained with the pH 7 55 reagent than with the 7 8 reagent

CLINICAL VALUE OF THE FLOCCULATION TESTS

In discussing the comparative value and clinical usefulness of these tests, one must first consider the purpose for which the tests are being used Thus, the test most frequently providing evidence of hepatic injury may be of the least assistance in differential diagnosis between intrahepatic and extrahepatic

obstructive jaundice The *strongly positive* thymol test is perhaps the most helpful single response as an aid in differential diagnosis as it is very *infrequent* in extrahepatic obstructive jaundice However these tests have been most helpful to us when their responses are considered together as a group, particularly those of cephalin cholesterol and thymol tests [9] When applied to all types of liver disease with jaundice negative responses with all the flocculation tests occur sufficiently often particularly with certain types of intrahepatic disease, that negative responses are not very dependable as aids in differential diagnosis between intrahepatic and extrahepatic obstructive jaundice This also is true, to a lesser extent when the cephalin cholesterol flocculation test alone is positive Certain group responses of the flocculation tests however occur much more consistently with jaundice of intrahepatic cause than with jaundice of extrahepatic cause and these strongly influence our diagnostic conclusions Positive responses with all of the flocculation tests constitute strong evidence in favor of an intrahepatic cause of the jaundice This group response has not been observed in any of our cases of uncomplicated extrahepatic obstructive jaundice of less than two months duration and has been observed in only 7 per cent of our cases of more prolonged or complicated extrahepatic obstructive jaundice In those cases of bile duct obstruction in which the responses were positive the clinical evidence of recurrent cholangitis and the picture of obstructive biliary cirrhosis aided in the diagnosis Perhaps even less common in extrahepatic obstructive jaundice is the occurrence of a negative cephalin cholesterol test in association with a positive thymol test (including positive thymol flocculation) The occurrence of this pattern of response thus appears to constitute strong evidence in favor of an intrahepatic cause of jaundice When the tests are used primarily to detect hepatic injury, the cephalin cholesterol test will give more positive responses when applied to all types of hepatic disturbance than will the thymol test However, in certain stages and types of hepatic injury the latter will be positive when the other is negative Thus both again are necessary for optimum information

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Thymol turbidity readings also vary with the pH of the thymol solution that is employed Thymol solutions at two different pH values are being employed, that originally recommended by Maclagan being pH 7 8, and one at pH 7 55 being employed by Mateer and his associates [15] One commercial concern recently has made available a thymol buffer adjusted to still another pH, namely 7 65 Recent studies in our laboratory indicate no special advantage of one pH over the other, the range of normal response varying, however, with the buffer used Thus, although the pH 7 55 buffer usually gives somewhat higher results, the upper limit of normal is also somewhat higher We, therefore, continue to use the pH recommended by Maclagan Mateer and his coworkers, however, feel that the more positive responses are obtained with the pH 7 55 buffer Recent studies of this question at the *U S Army Hepatitis* Center in Germany, carried out under the Commission on Virus and Rickettsial Diseases, tend to support the findings of Mateer and his associates In viral hepatitis, at least, more positive responses were obtained with the pH 7 55 *reagent than with the* 7 8 *reagent*

CLINICAL VALUE OF THE 'FLOCCULATION TESTS

In discussing the comparative value and clinical usefulness of these tests, one must first *consider the purpose for which the tests are being used* Thus, the test most frequently providing evidence of hepatic injury may be of the least assistance in differential diagnosis between intrahepatic and extrahepatic

and the portal vein the pressure in it (the coronary vein) may be perfectly normal even though splenomegaly develops

The only set of circumstances which would lead to esophageal varices without either splenomegaly or ascites would be thrombosis in the coronary vein itself which is not a common circumstance Splenomegaly and esophageal varices without ascites are less rare Smith and Farber[2] reported a series of such cases occurring in children with this symptomatology They believed that these constituted a distinct group within the syndrome described by Banti, and reported evidence that many of these children had thrombosis in the splenic vein A case apparently belonging in this group was reported by Dr Eleanor Stein and the author[3] in 1938

EARLIER TREATMENT METHODS

Undoubtedly, the common cause of portal hypertension is cirrhosis of the liver, and before going on to a consideration of the various procedures recommended in the last few years in this condition and their exact indications, it seemed worth while to review some of the earlier work in this field All the surgical procedures are aimed more or less at relief of symptoms Paracentesis abdominis is the commonest and probably the oldest procedure for temporary relief of ascites This procedure usually has to be repeated with increasing frequency and sometimes becomes impossible or unsafe due to the formation of adhesions Methods have therefore been developed to increase circulation between the portal and the systemic veins on the one hand or to provide internal drainage for the ascitic fluid on the other

The operations described by Talma and Morrison consist of laparotomy scarification of the parietal peritoneum and suture of the omentum against the scarified area Later this was modified by making retroperitoneal pockets into which the omentum was placed This was further modified by bringing the omentum out into the subcutaneous tissues Other surgeons performed splenopexy against scarified areas of the parietal peritoneum Still others made a retroperitoneal pocket into which the spleen was placed Omi developed an operation known as omento nephropexy in which the peritoneum over the kidney was opened, the kidney freed from surrounding fat and decapsulated The omentum was then sewed over and around the kidney

Another surgical procedure suggested was scarification of the liver on the undersurface of the diaphragm to promote adhesions in that area The suture of the gallbladder to the peritoneum was suggested by von Eiselsberg while Lanz[4] returned the right testicle and cord to the peritoneal cavity in the hope of aiding the absorption of fluid

In animals, collateral circulation for an obstructed portal vein can be produced by side to side anastomosis of the portal vein in the inferior vena cava This was first tried out by the Russian surgeon Eck [5] and is known as an Eck fistula Hesitancy in performing the operation in patients was due less to technical difficulties than to the fact that the dogs seldom survived for as long as a year following Eck fistula The first such operation in man was carried out by Rosenstein[6] and shortly after that Krestovsky[7] succeeded with

INDICATIONS FOR AND RESULTS OF SURGICAL PROCEDURES IN PRONOUNCED PORTAL HYPERTENSION

JONATHAN E RHOADS, M D

Interest in portal hypertension has been stimulated in recent years by the work of Blakemore and his associates[1] in New York on nonsuture anastomosis, on splenorenal anastomosis and on portacaval shunts

EFFECTS OF PORTAL HYPERTENSION

Portal hypertension is the term used to cover increases in intravascular pressure in any part of the system of veins flowing into the portal vein The parts of this system which are of particular interest are the left coronary vein of the stomach, the splenic vein and the superior mesenteric vein The pressure may be raised concomitantly in all of these divisions if the portal vein is obstructed within the liver as in cirrhosis or at the hilum of the liver where stenosis or clot formation may occur If there is obstruction as from a clot in the superior mesenteric vein caudad to the junction of the splenic vein, it is possible to have increased pressure in the superior mesenteric vein and its radicals with normal pressure in the portal and the splenic vein and the coronary vein of the stomach Such patients may have ascites, but would not be likely to have hemorrhage from the esophagus On the other hand, obstruction may affect the splenic vein causing congestive splenomegaly without hypertension in the intestinal branches of the portal system Whether esophageal varices develop in this situation depends on whether or not the coronary vein pressure is increased In some individuals, the coronary vein drains directly into the portal and is independent of the splenic vein, in others and probably more commonly, it drains into the splenic vein In this last situation, one needs to know whether the obstruction in the splenic vein is between the spleen and the point of junction with the coronary, or whether it is between this point of junction and the portal so that it would obstruct the flow not only from the spleen but also from the stomach and esophagus

To recapitulate, the three major effects of portal hypertension are ascites, esophageal varices and splenomegaly, all tend to result from generalized portal hypertension due to intrahepatic obstruction of the portal blood flow or obstruction of the portal vein at the hilum of the liver Ascites alone may result from obstruction of the superior mesenteric vein before it is joined by the splenic to form the portal Splenomegaly without ascites may result from obstruction in the splenic vein Esophageal varices result from increases in pressure in the coronary vein of the stomach which may be a direct branch of the portal or a branch of the splenic vein If it is a direct branch of the portal or if it joins the splenic vein between a point of obstruction in that vein

The drainage operations were, as a rule, of temporary benefit because the wicks sealed off, the glass buttons sealed off and the saphenous vein became occluded However, the glass tubes will sometimes work for a few months which may be sufficient for symptomatic relief in the late stages of the disease

PRESENT METHODS OF TREATMENT

In his present approach to this problem, Blakemore divides patients with signs of portal hypertension into those who have impairment of liver function indicating cirrhosis and those who do not In his last paper on the subject, Blakemore[11] does not lay down any definite criteria regarding the degree of liver injury which contraindicates operation He cites 3 patients who died of cholemia In the first case the patient had had acute hepatitis only three and a half months previously Necropsy examination of the liver revealed liver cell degeneration compatible with an active virus hepatitis He thought that they had possibly made a mistake in operating so soon He also notes that the patient s anorexia jaundice and ascites had persisted from the time of the acute hepatitis up to the time of operation Cephalin flocculation tests were persistently four plus in that patient There had been a reversal of the albumin-globulin ratio—albumin 1 9, globulin 4 4 there had been an elevated prothrombin time indicating a reduction of prothrombin to 50 per cent

The second of the 3 patients that died of cholemia in Blakemore s series had 40 per cent bromsulfalein retention after a half hour, cephalin flocculation ranged from three to four plus, the galactose retention remained elevated, prothrombin remained about 50 per cent In a third case a Salmonella blood stream infection developed during the convalescence and the patient died with jaundice No autopsy was obtained so that it is not possible to know just what happened in this case In the second case while the liver changes were severe, he noted that two other patients in the series had had about equally severe liver damage, but they had been prepared for a longer time with a high protein high carbohydrate diet and underwent operation successfully

While this whole field is in a state of flux, perhaps the present day plan of management may be outlined about as follows

Patients with bleeding esophageal varices ascites or both should be considered as possible candidates for surgical treatment

If liver function tests are normal the obstruction is probably extrahepatic and if the major symptom is hemorrhage from esophageal varices the recommended operation is splenorenal anastomosis with splenectomy If liver damage is present as indicated by tests, porta cava shunt is usually the preferable procedure This has been done most often by an end to side procedure dividing the portal tying the end toward the liver and anastomosing the other end to the side of the cava It also has been done by a side to side technic Blakemore thinks the latter is advantageous because it permits a larger anastomotic opening It does not completely stop the possibility of blood flowing to the liver or through the portal vein and in that regard lessens the chances for thrombosis in the portal radicals which he seems to feel is to be

such an operation in man, both of these operations were performed about 1900 to 1902

Vidal[9] and Bogoraz used a slightly different procedure They divided the superior mesenteric vein, ligated the *cephalad end and anastomosed the* caudad end to the side of the inferior vena cava These authors developed special instruments for the procedure and used a rubber covered clamp which occluded the portion of the vena cava where the anastomosis was being done, at the same time leaving a portion of the lumen of the vena cava open for the flow of blood Vidal's case had had hematemesis frequently before operation, hemorrhages and the ascites disappeared for over two months The patient had reactions after eating protein and, therefore, came to subsist largely on carbohydrates Four months after operation the patient had a sudden chill and died in twenty-four hours Vidal's report was in 1903

Most of these procedures seem to have been done only a few times and only in the case of the Talma-Morrison operation was a sufficiently long series accumulated to permit statistical evaluation In the report of W J Mayo,[9] 47 cases of this operation were done with 7 deaths in the hospital, 21 patients were alive at the time of the last follow-up, 1 after nine years, 1 after eight, 1 after seven and 1 after five years The operative mortality was 15 per cent, and 10 per cent of those that survived had lived five years or more At the time of the report, there were a number of cases still living that had not yet reached the five-year limit

Operations designed to provide continuous drainage of the ascitic fluid include lymphangioplasty, described by Handley, which consists of passing long threads from the peritoneal cavity under Poupart's ligament into the thigh In the procedure of Franke, sutures extended from the peritoneal cavity into subcutaneous tissues near the umbilicus In another procedure attributed to Routte, the saphenous vein was divided and the proximal end turned upwards and *the open end of the vein sutured into the peritoneal* cavity

Recently it has been suggested that one kidney be sacrificed and its pelvis be anastomosed to the peritoneal cavity so that the ascitic fluid can flow down into the bladder[10]

Another maneuver which some surgeons have employed is the large scale removal of parietal peritoneum so that the bowel will become adherent all along the under surface or the anterior side of the peritoneum The aim of this operation is both to establish better collateral circulation and also to permit direct drainage of fluid into retroperitoneal tissue

An old operation which is still practiced occasionally in bad risk patients in whom it is thought nothing more can be done, is the introduction of short glass tubes extending between the peritoneal cavity and the subcutaneous tissues in order to permit the more or less continuous passage of ascitic *fluid* into the subcutaneous tissues where it can be better absorbed

It is evident from this brief review that the principles now employed in the surgical treatment of portal hypertension were recognized many years ago and that the first caval anastomoses were performed almost half a century back

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avoided It should not be done if the patient has, or has recently had, an infectious hepatitis No operation should be done under those circumstances

In general, if the bromsulfalein retention is over 40 per cent, if the cephalin flocculation is persistently four plus, if the prothrombin cannot be maintained at 50 per cent or above, operation should be preceded by a protracted trial of medical therapy during which a high caloric intake is insisted upon with a large intake of carbohydrate, 20 to 25 per cent of the calories as protein and a very low intake of fat

Operation should be performed either under cyclopropane anesthesia or under continuous spinal anesthesia with careful control of the blood pressure to prevent any period of hypotension

TYPE OF OPERATION

Final decision about the type of operation usually rests upon the determination of venous pressures in the various parts of the portal system at operation These are determined by injecting saline slowly through a fine needle into the branches of the veins concerned A manometer is connected to the tube between the syringe and needle so that the pressure required to make the saline flow into the vein may be accurately measured The first measurement is usually taken from a branch of the superior mesenteric vein If this is not elevated, the obstruction is in the splenic or coronary vein or both and branches of these veins are tested If the pressure is high in the splenic vein but not in the coronary vein, simple splenectomy is indicated The pressure in the splenic vein should be tested at a point between the spleen and any possible junction of the coronary with the splenic vein If the pressure in the coronary vein is elevated and the pressure in the superior mesenteric vein is not, splenorenal anastomosis is to be preferred If, on the other hand, the pressure in the superior mesenteric is elevated and the pressure in the portal is then checked and found normal, a block is indicated in the superior mesenteric In other words, the obstruction is caudad to the junction of the splenic and superior mesenteric to form the portal and under those circumstances an anastomosis of the superior mesenteric vein peripheral to the block to the vena cava is usually indicated

Splenectomy alone, if done in patients with increased pressure in the coronary vein of the stomach, will not, in general, prevent further hematemesis, and this operation usually prevents subsequent splenorenal anastomosis

Blakemore stresses this point considerably because he feels that these patients who have a block in the veins that drain the esophageal veins do not do well with a direct portacaval shunt but require a splenorenal shunt He believes that a good many past failures are related to the fact that the spleen was taken out first, and it was then not possible or practical to do an anastomosis to the left renal vein

RESULTS

What can be said regarding the results? In the Presbyterian Hospital[11] series, 58 patients have had shunts, 11 have died, 3 of cholemia, 2 of cerebral

damage, 1 of cardiac failure 3 of mesenteric thrombosis, 1 from intra peritoneal hemorrhage and 1 from gastrointestinal hemorrhage This makes an over all mortality of about 19 per cent Of the 35 patients who gave a history of severe attacks of gastrointestinal bleeding before the establishment of portacaval shunts, 11 had one or more attacks of hemorrhage following discharge from the hospital The follow up was only a few months in some of these cases Analysis of these 11 cases revealed that 5 had had previous splenectomies, 4 of the 5 had extrahepatic blocks making it not feasible to employ the splenic vein in establishing a shunt to the left renal vein In 2 other cases of these 11 the splenorenal anastomosis failed to work This was attributed to the development of a low grade infection in one case The other came into the hospital with acute bleeding throughout the intestinal tract and it was found that the common duct was completely filled with stones

Without going into technical details it would seem from Blakemore's report, and from the experience of others, that there is a decided tendency toward suture anastomosis rather than use of the vitallium tube splints which Blakemore and Lord[12] introduced for blood vessel anastomosis in 1945

In the entire series of 58 cases 16 were due to extrahepatic portal block and 42 were due to intrahepatic block In the series of 58 cases portal caval anastomosis was done 9 times with 1 postoperative death, 3 cases had a three year follow up and a fourth case is now nearly three years In these cases no essential differences were noted in the behavior of the cirrhosis either clinically or chemically from a comparable group of cases in which splenorenal shunt was performed The complete details on the all important matter of liver function changes apparently have not as yet been published in the New York series

Dr Harold Zintel reported a case at a meeting of the Philadelphia Academy of Surgery in 1947, in which he had repaired a stricture of the common duct and done a portacaval shunt At the end of nine months, liver function tests indicated improvement although there was some persistent impairment as one might expect It is difficult in this case to know which phase of the operative procedure might be responsible for the improvement, whether the correction of the stenosis of the common duct or of the relief of portal hypertension, but at least it seemed evident that the establishment of the portacaval shunt had not led to an early downhill course such as that noted by various authors in experimental animals with Eck fistulas

SUMMARY

Some of the available information about portacaval shunts has been summarized It is important to emphasize that in addition to portal hypertension due to hepatic cirrhosis there are also cases of portal hypertension due to extrahepatic obstruction It is necessary to localize as accurately as possible the position of the block before deciding whether to do a portacaval shunt, a splenorenal shunt or simply a splenectomy for the removal of a large congested spleen

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PANEL DISCUSSION

Question What diseases of the liver other than hepatitis give a divergence of non-protein nitrogen and urea nitrogen values?

Dr Balduin Lucke Any disease in which liver tissue is destroyed it doesn t matter how it is destroyed, whether by chloroform or carbon tetra chloride, because urea is formed within the liver Destruction of the liver therefore will mean an absence of urea formation Some urea may still be in the body, hence it doesn t disappear entirely With regard to non protein nitrogen, the nitrogen rise is of the same order as the non-protein nitrogen rise which occurs during resorption of an exudate or the destruction of a large mass of cells

Question Does the use of gamma globulin affect the pathologic picture in hepatitis?

Dr Lucke I don t know I think there s no doubt in the world that this globulin has done a great deal of good and should be used, but I don't know how it affects the pathologic picture I doubt whether it affects it to any extent

Dr Bockus Do you want to add anything, Dr Neefe, at this point?

Dr Neefe No, I concur

Question Is the mortality higher in homologous serum jaundice than in infectious hepatitis?

DR LUCKÉ Probably But remember this we know that if we take a large number of cases of homologous serum jaundice, we are dealing with patients who have received repeated transfusions of blood because they were sick before the occurrence of jaundice, now to what extent the preceding disease affects the severity of the homologous serum jaundice we don t know but taking it by and large, there does seem to be a difference in the mortality rate

Question What is the pathology in the pancreas in hepatic necrosis?

DR LUCKE None In the vast majority of cases the pancreas is perfectly normal Occasionally when there is very marked ascites there is edema not only of the pancreas but in a number of other organs The pancreatic veins drain their fluid into the portal vein as you know Hence if there is any interference with the portal flow, there may develop congestion and edema of the pancreas but there are no other significant changes

Question Does a change in the albumin globulin ratio produce any characteristic change in the responses to the flocculation tests?

DR NEEFE One would have to answer this by saying that there is no consistent relationship between the quantitative amounts of protein demonstrated in serum and the responses of the test One can have a reversed albumin-globulin ratio, for example in nephrosis and have negative flocculation It may be reversed in certain types of cirrhosis of the liver and the cephalin-flocculation may be positive and the thymol negative In other cases with the same quantitative changes in ratio all the tests may be positive Thus I think one would have to say there is no direct relationship and that qualitative changes probably are more important than the quantitative changes

Question Have you observed a higher incidence of intrahepatic obstruction in cases of homologous serum jaundice as compared with infectious hepatitis?

DR NEEFE I know of no data that would actually permit a comparison of the incidence of intrahepatic obstruction in the two types In the first place, we often do not know which type of hepatitis we are observing in patients that we see in the hospital Certainly the picture of intrahepatic obstruction can occur in either type but I don t know whether it s any more frequent in one than in the other

Question How long must one wait to use blood from a person who has had infectious hepatitis as a blood donor?

DR NEEFE That of course, is a question that is always raised and one for which there is as yet no answer No one knows how frequently one who has had viral hepatitis continues to carry the virus Probably the person who carries the virus but who has never had the recognized disease is more dangerous We are not even certain that the person who has had the acute

disease in a clinically recognizable form is infectious after the jaundice has subsided, only very limited experimental studies have been made Blood has been obtained from three or four volunteers following recovery and has been injected in volunteers None of these bloods proved to be infectious under the conditions of the experiment However, it may be much like typhoid where one would have to test specimens from 40 or 50 persons after hepatitis to determine this As this requires human volunteers at present, it has been impossible to date Actually each blood would have to be tested individually because, as soon as one pools the specimens, one would risk the chance of neutralizing any virus that might be present in one specimen by antibodies in the other So I m afraid this is an unanswerable question, now From a practical viewpoint, one can only say that, insofar as possible, it perhaps is a little safer not to use donors who have had hepatitis

Question How frequently are we seeing homologous serum hepatitis since the end of the war?

DR NEEFE Again, I think it is difficult to cite actual figures In most hospitals, no records are being kept in reference to this question Cases are not reported to any one center and it is often impossible to definitely establish the diagnosis In the University Hospital we are seeing a rather surprising number of patients who have jaundice following receipt of some blood product, particularly in surgical patients I m afraid I can t actually cite any figures, much depends on the frequency with which the plasma is used in the various institutions In the University Hospital very little pooled plasma is used at the present time Most of the cases we see come from other sources where plasma has been used One has to remember that whole blood also is capable of transmitting virus and a certain number of cases are occurring from this source

DR BOCKUS I think I m right in saying that a survey made by Dr Rosenthal about two years ago suggested that approximately 5 per cent of patients receiving blood or plasma at the Graduate Hospital developed what we thought to be homologous serum jaundice It is my impression that most of these patients had received only blood In going about the country, I have been impressed with the reports of a rather high incidence of the homologous serum hepatitis in the various hospitals Dr Neefe, would you like to say a word about its prevention?

DR NEEFE It may be worth just mentioning recent figures from England on this problem before discussing the matter Dr Bockus has raised Dr MacCallum of England visited here in the Spring and had with him some unpublished data from the most recent survey made in England regarding the incidence of the hepatitis following blood and plasma These data were broken down into incidence in relation to large plasma pools, small plasma pools and whole blood They found about a 12 per cent incidence of hepatitis in relation to large plasma pools, that is, pools composed of plasma from a thousand or more donors With small plasma pools representing 10 to 25 donors, the incidence was about 6 per cent, comparing favorably with figures

obtained in this country In connection with whole blood, their incidence was about 1½ per cent

In respect to prevention, the first and most obvious method is to avoid the use of blood and its products except where there is a real indication Obviously there are many indications so that we just can t get along without blood in many instances

Thus attempts have been made to find some method for sterilizing blood and its products Recently a number of groups have been working with improved equipment for applying ultraviolet irradiation to blood plasma Whole blood will not stand the sort of treatment that plasma will and plasma won t stand the sort of treatment that albumin will One can heat albumin solutions for ten hours at 60 C and this apparently inactivates hepatitis virus Most of the albumin that one can obtain at present presumably is safe because it has been so treated Plasma containing viruses other than hepatitis virus apparently can stand an amount of irradiation which does not cause serious changes in the electrophoretic pattern or render it antigenic but inactivates the viruses mentioned The only way, of course of studying hepatitis virus is in human volunteers Dr Joseph Stokes, Jr and Dr Mercer Blanchard recently had plasma known to contain hepatitis virus irradiated by this technic and tested it subsequently in a group of volunteers The irradiation apparently was effective in killing the virus under those conditions as hepatitis did not develop, whereas the controls who received the same material but not irradiated had incidences of 50 to 60 per cent There is some hope, therefore, that ultraviolet irradiation may be useful for this purpose although it is not an ideal method and is technically inconvenient and tricky

The use of irradiated plasma, therefore, may perhaps be warranted under controlled conditions I don t believe it should be regarded as perfectly safe just because it has been irradiated as the preliminary studies to date have been concerned with only one strain of hepatitis virus

Question If carbohydrates form fat, why give the patient with liver disease large amounts of fat? How much fat do you give your hepatitis cases?

DR JAMES F MONAGHAN I did not wish to imply that large amounts of fat are deliberately prescribed but that an extremely low fat diet formerly recommended is not required I think that the average patient with liver disease can handle a perfectly normal, well balanced diet and does much better on such a diet than on one devoid of fat

DR BOCKUS Is there any disadvantage in allowing even average amounts of fat during the stage of deep jaundice?

DR MONAGHAN During this stage of the illness when there is a lack of bile in the digestive tract fats are poorly tolerated

Question Did you mention that you thought that the slow continuous intravenous drip of glucose in acute fulminating hepatitis—infectious or otherwise—is at times lifesaving, or don t you believe that?

DR MONAGHAN I m afraid I don t believe it I ve done it naturally, but doubt that it is lifesaving

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established About 35 to 50 per cent of the patients who have itching from intractable jaundice will get some symptomatic relief from gynergen The only way that that can be determined is by trial in individual cases In some patients it has to be continued for some time and, of course, is not altogether without danger Otherwise the administration of large amounts of glucose intravenously might be of some value I have never seen any particular benefit from calcium I ve never seen any specific benefit from any of the ordinary sedatives I ve had a little experience with the administration of novocain intravenously It has given some relief temporarily during the time of administration, but it's purely a symptomatic relief The suggestion of producing surgical drainage in these patients i e external drainage of the bile, I don t think has a great deal to recommend it A great many of these patients who have itching have what seems to be a fair amount of bile flowing into their intestinal tract, so that I don t think that the production of an external biliary fistula will accomplish very much I don t know of any specific treatment for the itching I have used histamine without much result Various antihistaminics have been tried and I have never been able to satisfy myself that they have any specific value

Question How harmful are barbiturates, opiates and demerol to a liver damaged by jaundice due to biliary obstruction?

Dr Tumen That s a rather difficult question to answer I don t know that these substances are specifically harmful to the liver itself I think that in the presence of very severe liver damage the various sedatives that have been mentioned are probably not detoxified satisfactorily and are potentially harmful I think that morphine and other opium derivatives, the alkaloids of which are normally held up in the liver, or conjugated or destroyed by the liver can be definitely detrimental to a patient who has severe liver damage They have to be used with a great deal of caution The various long acting barbiturates also theoretically are handled with difficulty in some instances of liver damage and I think a great deal of caution has to be used From a practical standpoint, the choice of a sedative sometimes presents great difficulties Opium should be avoided as much as possible The very short acting barbiturates can probably be used with a reasonable amount of safety I myself feel that some of the drugs that have a bad reputation like paraldehyde, probably can be handled a little better by some of these livers than we used to think and I ve recently used some in patients without any particular difficulty whatsoever

Question What is the present status of intravenous albumin in the therapy of liver disease?

Dr Neefe The present status is greatly influenced by its availability I think that there s no doubt that it can be very useful as a temporary aid at least in getting over certain critical states

The chief disadvantage is the fact that it s just not available in adequate amounts except on an experimental basis Large amounts are often required and the total cost of the amounts needed for one case may be rather fantastic

DR BOCKUS Did you ever see a patient die in a hypoglycemic condition—in acute hepatic coma?

DR MONAGHAN Yes, I have, but I have not saved any such patient with continuous glucose infusions

DR BOCKUS How do you know you haven't?

DR MONAGHAN The ones I felt definitely were going to die did so in spite of this form of therapy

Question Is there any possible injurious effect of using intravenous amino acids in cases of acute severe liver damage? Would you depend entirely on glucose and carbohydrate in these cases?

DR MONAGHAN For parenteral therapy I depend entirely on glucose, plasma, and whole blood I am afraid of the use of intravenous amino acid solutions in very acute liver disease Amino acids are probably not conjugated by the acutely damaged liver

Question Do bile salts and other cholagogues stimulate bile production or merely increase secretion?

DR TUMEN The answer to this is that they do both, but the strongest stimulant to the formation of bile, and to the further formation of bile salts, is the bile salts themselves The bile salts are able to stimulate the formation of additional bile acids, to stimulate the flow of fluid from the liver, and also are able to stimulate the passage of material from the liver into the duodenum, so that I would say that they do actually increase the amount of secretion from the liver and the actual total formation of bile Whether they have therapeutic value or not, is another matter

DR BOCKUS Do you classify them as Dr Ivy does into choleretic and hydrocholeretic types?

DR TUMEN Yes There is supposed to be a difference in function of the various bile salts, some are supposed to have definite choleretic action in the sense that they increase bile formation and some are supposed to have hydrocholeretic action in the sense that they stimulate fluid flow, and then some of them are supposed to be cholagogues, but I don t know of any body else other than Dr Ivy who has definitely proved that the bile salts are so specific in their action

Question Discuss the management of intractable itching in jaundice due to chronic cholangitis secondary to longstanding biliary obstruction The jaundice has been surgically relieved, there is no response to parenteral calcium or gynergen

DR TUMEN Unfortunately, I don t know any specific for the intractable itching that's seen in some patients who have jaundice I think myself it s a manifestation of severe liver damage I don t think that it s due to the retention of any particular thing in the bile, or to the presence of any particular constituent of bile in the blood Whether it's due to the inability of the liver to destroy certain cholinergic substances or not, I don t think is entirely

established About 35 to 50 per cent of the patients who have itching from intractable jaundice will get some symptomatic relief from gynergen The only way that that can be determined is by trial in individual cases In some patients it has to be continued for some time and, of course is not altogether without danger Otherwise the administration of large amounts of glucose intravenously might be of some value I have never seen any particular benefit from calcium, I ve never seen any specific benefit from any of the ordinary sedatives I ve had a little experience with the administration of novocain intravenously It has given some relief temporarily during the time of administration, but it s purely a symptomatic relief The suggestion of producing surgical drainage in these patients, i e external drainage of the bile I don t think has a great deal to recommend it A great many of these patients who have itching have what seems to be a fair amount of bile flowing into their intestinal tract, so that I don t think that the production of an external biliary fistula will accomplish very much I don t know of any specific treatment for the itching I have used histamine without much result Various antihistaminics have been tried and I have never been able to satisfy myself that they have any specific value

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In spite of that there are certain situations, in which there is a hope that if the patient can be pulled through a temporary crisis there is a chance of survival, where albumin is one of the most useful measures available It's the natural protein of the blood, it seems to promote diuresis, and helps to sustain the circulation I personally regret the fact that we don't have it more easily available In liver disease in particular, the situation is a little different than with nephrosis where administered albumin may be lost through the kidneys True, it is lost in the body fluids, ascites and pleural fluid, etc, but if these decrease or are not present, much of the albumin may be utilized

Question In severe, acute, hepatic necrosis may not a high caloric intake overwhelm and exhaust the liver and further damage it by raising its metabolism?

DR MONAGHAN In acute, severe, hepatic necrosis I doubt that it would be possible to get a high caloric intake into the patient These patients are very ill and many times are in coma As a general thing if the patient is capable of handling a high caloric diet you're not going to overburden the liver The liver will only utilize what it is capable of utilizing, so that food that is ingested and cannot be handled by the liver, would just be wasted to the body If the liver is necessary in its utilization, I don't see how you could possibly do it damage

DR BOCKUS Anything you'd like to add to this, Dr Neefe?

DR NEEFE I don't think there's much to add except that I suspect that in temporary states of acute hepatic insufficiency, the administration of larger than normal amounts of protein actually may be harmful during the critical period Placing a greater strain on the liver than it normally has possibly may lead to incomplete metabolism which may not be favorable to survival After the critical state is over, of course, the situation is different

DR MONAGHAN I think that any deleterious effect exerted under these circumstances, Dr Neefe, would be the result of disturbing water balance, which might be associated with other evidences of shock Certainly the dumping of solutions not isotonic or in too large amounts into the stomach by tube can bring about harmful effects at times

DR NEEFE That's right, exactly

Question How useful is the urine urobilinogen test in the early diagnosis, pre-icteric stage and in following the clinical course of acute infectious hepatitis?

DR NEEFE The positive urine urobilinogen test is very helpful, but the appearance of urobilinogen is notoriously irregular both in the pre icteric stage of hepatitis and during the course of other types of liver disease A negative test thus means little, if it is positive, it's helpful It's a simple test and therefore of value, but in the pre-icteric stage of hepatitis, for instance, urine bilirubin often appears earlier and once it appears it usually stays there for a time

DR BOCKUS How much urine bilirubin do you have to have in the urine

for the froth to be colored so that the physician without tubes and things can recognize it, in a nice clear light? Did you ever investigate that?

Dr Neefe Only in a gross way It s very difficult to quantitatively measure amounts of bilirubin in the urine By the time the foam is well colored there usually will be at least subclinical jaundice, that is, the serum bilirubin will be somewhat elevated The Harrison spot test usually will be positive for several days before the foam test is positive

Dr Bockus But still it s detectable in the froth often before you can notice the presence of clinical icterus?

Dr Neefe Yes, that s right

Question What is the probability of transmitting homologous serum hepatitis in mass immunization using large syringes and individual needles?

Dr Neefe The question here relates to the use of a large syringe and merely changing needles between patients There has been evidence to indicate that hepatitis has been spread from person to person by that technic e g , in penicillin therapy in large hospitals There is at least one outbreak which was presumed to have been spread in that way The personnel administering such medications usually are trained to aspirate before they inject This may lead to contamination of the entire syringe content There was a very serious outbreak of streptococcal infections in one hospital with 2 deaths which originated in this way Thus there is a definite risk involved

Presentation of Cases

GASTROENTEROLOGICAL CONFERENCE

GRADUATE HOSPITAL STAFF

DR JOHNSON (*Case 1*)

The first case for presentation this afternoon has to do with a forty-eight year old white man who reported to the office on November 16, 1948, with the following story

He is said to have had symptoms suggestive of peptic ulcer at the age of fifteen years At the age of twenty six years, in 1926, vomiting evidently became quite troublesome and he had a gastrojejunostomy performed at a *hospital in this city Apparently the operation proved successful because he* became asymptomatic He ate everything and followed no diet Occasionally two or three times a year over a period of two or three days, he would have slight heartburn which would subside spontaneously, so that he was quite well from 1926 until October 11 1948 when in the evening he vomited about 1½ pints of blood at an hour close to midnight He subsequently noted melena which was present over a period of about a week

The patient was admitted to another hospital that evening by his family doctor where he remained for twelve days While there he was transfused and before discharge x rays were taken which Dr Finkelstein will comment on a little later He came to see us about one week later because his physician had suggested that he needed an operation He wished another opinion He was quite free of symptoms at this time

DR FINKELSTEIN This patient was first x rayed elsewhere on October 19 1948 The most representative films of that examination are illustrated in Figs 191 to 193, inclusive

Figure 191 reveals a functioning gastroenterostomy, but the fluoroscopic notes state that not much barium left the stomach by that route The antral portion of the stomach seems pulled to the right and upward suggesting that it is adherent to the gallbladder bed Increased density of the barium shadow in the latter area indicates that the antrum is also deviated posteriorly, as is also demonstrated in subsequent lateral projections The antrum is therefore slightly folded upon itself If this is borne in mind perhaps it may help to explain certain peculiar configurations which are seen later

Figure 192 is a set of serialograms of the gastroduodenal area made in a lateral projection Because it has been displaced to the right and posteriorly, when distended with barium the gastric antrum obscures the first portion of the duodenum (lower pair of exposures) When the antrum is contracted (upper pair of exposures) the first part of the duodenum is seen, but the bulb

exhibits such a marked degree of irregular contraction that its exact limits are difficult to establish Furthermore, the deformity of the bulb is not typical of any particular etiologic agent The second portion of the duodenum does not contain barium at this time, but the third and fourth portions are partially outlined and are grossly negative No barium can be definitely identified in the biliary tract

Figure 193 is the appearance presented late in the examination, when the stomach has almost completely emptied itself of barium A linear collection of barium is observed in the usual location of the common duct, and a thin faint streak of the opaque material continues in a direction toward the ampulla

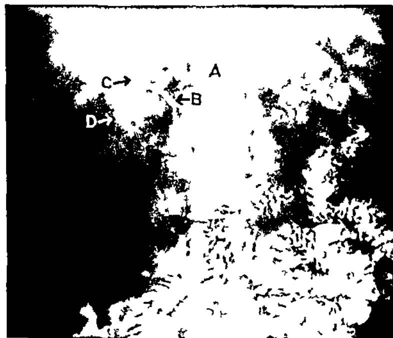


Fig 193 An exposure made later during the examination of October 19 when the stomach is practically empty A few flecks of barium are in the stomach A The com com duct B is clearly outlined by barium C probably is the cystic duct D represents barium in the proximal descending portion of the duodenum

A corkscrew like arrangement of barium suggests that the cystic duct also contains some of the contrast medium How did the barium enter the biliary tract? No fistulous communication between it and the stomach or duodenum has been identified Whether the barium could have regurgitated from the second portion of the duodenum into the ampulla and thence into the ducts, or whether there is an actual fistulous communication at the ampulla, also remains in doubt In view of the marked deformity of the duodenal bulb it is most likely that there is a fistula between it and some portion of the biliary tract However, the presence of such an abnormal communication is merely inferred not proved by this study

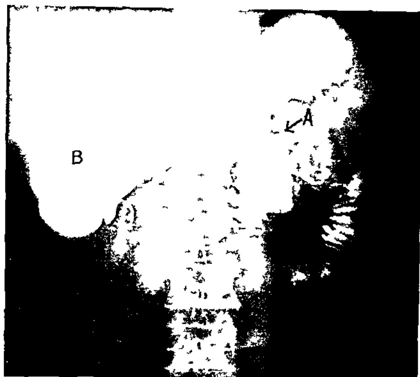


Fig 191 First barium meal examination made elsewhere October 19 1948 A functioning gastroenterostomy B antrum pulled to the right and posteriorly producing large globular white shadow

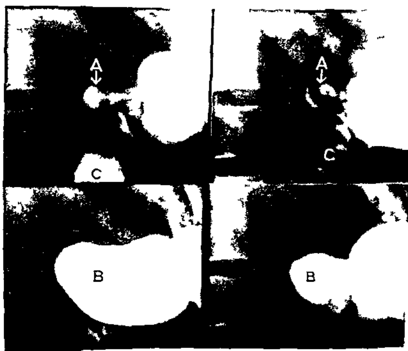


Fig 192 Serialographic exposures of duodenal cap and gastric antrum in lateral projection October 19 The deformed cap, A is frequently obscured when the antrum B is distended A small amount of barium is present in the duodenal loop C

well filled with barium and are not dilated No radiolucent filling defects, such as might be produced by biliary calculi, are seen It is noteworthy that the lower third of the common duct does not contain barium, which is fairly good evidence that the opaque material did not enter the duct by regurgitation through the ampulla

In Figure 196 in addition to barium in the ducts one sees just to the right of the gastric antrum a peculiar granular collection of barium, *B*, measuring approximately 2 by 3 cm This seems to be the fundus of a rather small gallbladder Extending medially and somewhat upward from it there is a faint trace of barium in what is probably a contracted neck of the gallbladder and

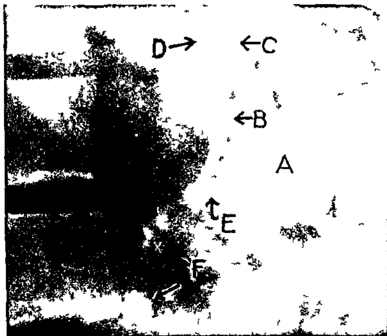


Fig 195 A lateral view of the gastroduodenal area discloses the gastric antrum A the common duct B the common hepatic duct C the cystic duct D the small deformed duodenal cap E and the second portion of the duodenum F It is noteworthy that the lower and ampullary portion of the duct is not filled with barium

in the cystic duct Still the precise route by which the barium has entered the biliary system has not been proved

Figure 197, a prone exposure made somewhat later in the examination, discloses a peculiar globular radiolucence *D* presenting a thin radiopaque periphery A few flecks of barium within the radiolucency do not form a recognizable mucosal pattern This is the typical double contrast picture of a hollow structure filled with air but presenting a thin surface coating of barium It is distinct from the outline of the barium containing gallbladder *B* During this latter period of observation the globular radiolucence is visible in most but not all projections At no time is it identified separate from the

The next x-ray examination was a barium meal study made one month later, November 19, 1948, at the Graduate Hospital The fluoroscopic observations were very confusing, as a result of which many films were exposed in various projections, the most important of these are shown in Figs 194 to 198 inclusive At the time of this second examination approximately half of the barium meal left the stomach via the enterostomy We were less successful in demonstrating the duodenal bulb, but found more barium in the biliary tract



Fig 194 Second barium meal examination made at the Graduate Hospital on November 19 1948 The duodenojejunal angle is at approximately A A functioning gastrojejunostomy is seen at B The duodenal loop (questionably expanded) is indicated by C The gastric antrum D obscures the duodenal cap This exposure was made early in the examination with the patient standing The following Figs 195 to 198 were also a part of the examination of November 19

Figure 194 is an exposure of the stomach and duodenum made in the erect position Although the duodenal loop is not actually expanded, it has a rather smoothly rounded configuration as if the pancreas is slightly enlarged It is not a clear cut observation and is not seen in other projections, but it is enough to arouse one s suspicion in a complicated situation

Figure 195 is a lateral view of the gastroduodenal area exposed when the antrum was partially contracted so that the markedly deformed and contracted first portion of the duodenum is visualized, presenting little change as compared with the examination made one month earlier The upper two thirds of the common duct, the cystic duct and the common hepatic ducts are now

well filled with barium and are not dilated No radiolucent filling defects, such as might be produced by biliary caculi, are seen It is noteworthy that the lower third of the common duct does not contain barium, which is fairly good evidence that the opaque material did not enter the duct by regurgitation through the ampulla

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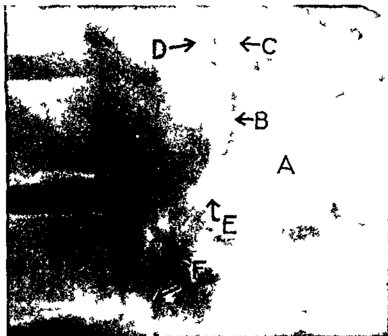


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Fig 196 Barium outlines the common duct A the gallbladder B and the cystic duct C The gastric antrum D obscures the duodenal cap



Fig 197 Later the same day additional barium was given to permit further study This figure is labelled to correspond with Fig 196 The arrows extending from D point to peculiar globular partly radiolucent shadow which is evidently the gastric antrum containing air and a mucosal coating of barium

outlines of the gastric antrum There is little doubt that it is in fact due to air trapped in the sharply angulated antrum where it is probably adherent to the inferior margin of the liver It seems to correspond with *D*, Fig 196, when the antrum was filled with barium instead of air

Before concluding this presentation it should be stated that prior to the second barium meal an attempted cholecystogram, by the doubly intensified oral method using twenty tablets of Priodax, failed to visualize the gallbladder or biliary ducts Incidentally, the various films exposed during the course of

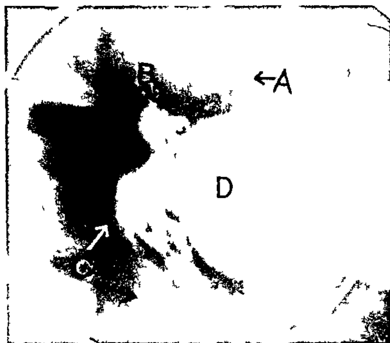


Fig 198 In a sharply oblique projection the antrum D no longer contains air and no accessory pocket lies near the antrum except for the projected shadow of barium in the gallbladder B The duodenal loop is fairly well visualized and is essentially negative

that protracted attempt at cholecystography failed to disclose any gas in the gallbladder or ducts

A summary of the objective roentgen findings includes the following features There is a well functioning gastroenterostomy without gastric resection The antrum is displaced to the right and is angulated posteriorly The duodenal cap is visualized with difficulty but is obviously markedly deformed and contracted No ulcer crater is demonstrated in the duodenal cap nor at or adjacent to the gastroenterostomy The configuration of the duodenal loop is within normal limits Barium from the gastrointestinal tract enters the biliary ducts and gallbladder, but the exact site of communication has not been identified with certainty

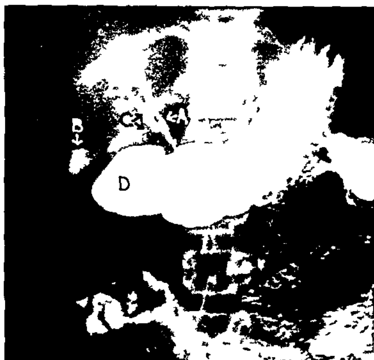


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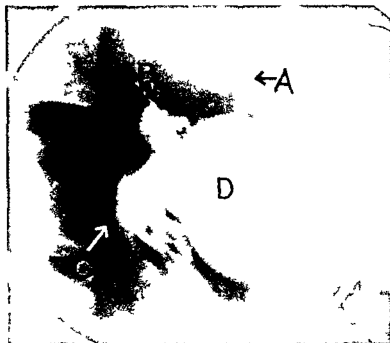


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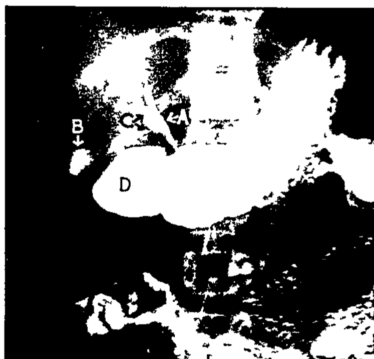


Fig 196 Barium outlines the common duct A the gallbladder B and the cystic duct, C The gastric antrum D obscures the duodenal cap



Fig 197 Later the same day additional barium was given to permit further study This figure is labelled to correspond with Fig 196 The arrows extending from D point to peculiar globular partly radiolucent shadow which is evidently the gastric antrum containing air and a mucosal coating of barium

when it is not distended to its greatest capacity a part of its marginal outline is made by the superimposed shadows of barium in the gallbladder, *B*, and in the second portion of the duodenum C, as seen in Fig 198

DR BOCKUS Since by cholecystography the gallbladder does not function yet it does partially fill with barium when given by mouth some consideration must be given to cholecystoduodenal fistula to account for these bizarre x ray findings The most common type of fistula between the upper gastro intestinal tract and biliary tract is cholecystoduodenal fistula, choledochoduodenal fistulas occur much less frequently We have an indication here that barium does fill what appears to be the main bile duct and some of it gets into the gallbladder Most of duodenobiliary fistulas are the result of primary gall tract disease i e, cholelithiasis When the gallbladder forms a fistula with the duodenum, usually a fistulous tract intervenes I should like for Dr Finkelstein to give this mechanism some consideration There is something about these films that causes one to wonder whether the entire segment of the long thin barium shadow is only the cystic duct There is something peculiar about the bifurcation of shadows which I do not understand Isn t it possible that a part of the linear shadow may represent a fistulous tract rather than the cystic duct?

The history is not suggestive of a primary *choledocho*duodenal fistula Classically a definite history of obstructive jaundice prior to the establishment of the fistula should be present In the absence of jaundice, duodenal ulcer would be a more likely cause of a fistulous communication between the common duct and the duodenum Regardless of the origin of a duodenobiliary fistula it is usually associated with a marked inflammatory reaction Symptoms simulating a posterior wall perforated duodenal ulcer and or pyloric obstruction often occur If we can rely on the history in this patient, the absence of jaundice, and of the symptoms mentioned, would be somewhat against the recent occurrence of an acquired duodenobiliary fistula Incidentally massive upper gastrointestinal hemorrhage does occur in association with the establishment of some fistulous communications due to erosion of a stone into the duodenum

Obviously some consideration must be given to duodenal ulcer disease to explain this situation Early in life symptoms were present suggesting duodenal ulcer A gastroenterostomy was performed and the ulcer like symptoms disappeared Now the patient has a contracted duodenal bulb It is conceivable that an ulcer may have perforated directly or by way of fistulous tract into the common bile duct or the gallbladder If we assume that an acquired biliary duodenal fistula really exists I believe that the recent hemorrhage cannot be considered as favoring the diagnosis of either primary biliary tract disease or primary duodenal ulcer The presence of a fistula, regardless of the mecha nism could account for the bleeding It is also conceivable that bleeding may have been due to a superficial duodenal ulcer or superficial ulcer or erosions in the stomach and not be in any way related to the fistula Indeed the absence of other symptoms in association with the hemorrhage would favor this the is

If we failed to give consideration to the strange distention of the antrum

The problems of interpretation may be summarized as follows The displacement and configuration of the gastric antrum can be safely attributed to congenital or acquired adhesions, more likely the latter The deformity and contraction of the duodenal cap might be explained as the result of primary intrinsic inflammatory disease, or secondary involvement by an extrinsic inflammatory process (such as might arise in the biliary system), or a combination of both factors Although we do not have specific information regarding the findings at operation in 1926, it is probable that the gastroenterostomy was performed because of a duodenal ulcer It is therefore also probable that the duodenal cap was thereby scarred and deformed for many years prior to the recent episode The present problem seems to be whether a recent exacerbation of duodenal ulceration was followed by local perforation into the common duct, or whether inflammatory involvement of the gallbladder or ducts eventuated in a fistula extending into the duodenum The roentgen findings leave little doubt that a fistula exists between the duodenal cap and the common duct, even though the actual communication has not been clearly demonstrated The possibility of a malignant etiology, such as a carcinoma of the pancreas, has not been excluded with certainty but is unlikely because of the absence of pressure deformities of the duodenum or antrum, and also because of the acute onset of the symptoms For similar reasons and because of its extreme rarity, primary malignancy of the duodenal cap does not merit serious consideration

DR BOCKUS Before you leave, Dr Finkelstein will you please make some additional comment about the pouch-like structure which seems to overlie the gastric antrum (*D*, in Fig 197)? Can you tell us more about it?

DR FINKELSTEIN Perhaps I can at least describe it more clearly It is a rather smoothly oval radiolucency about 4 cm in greatest diameter, presenting a thin radiopaque periphery Within the radiolucency there are a few faint streaks and flecks of barium coating the lining membrane of this structure, resulting in a fine "cobblestone" or reticular pattern We have seen a similar pattern in a few instances in the past when a fistulous communication with the intestinal tract has produced a double contrast shadow of the gallbladder by permitting air and a little barium to enter it In the present case the gall bladder has been rather definitely identified (*B* in Figs 196 and 197) some distance from the globular shadow now under discussion If the latter were a large duodenal diverticulum, it should be seen best in an oblique or lateral view such as Fig 198, but it is not It changes in size in various erect and recumbent exposures (not illustrated) so that it cannot be considered an accessory pocket due to a localized perforation of an antral or duodenal ulcer In no position or projection can it be separated from the lower portion of the stomach Therefore I still believe that it is gastric antrum which in this part of the examination happened to have some air trapped in it

DR BOCKUS Do you mean that the entire shadow (*D* in Fig 198) is antrum?

DR FINKELSTEIN For the most part, but not entirely The antrum has been twisted and is probably fixed in position by adhesions When completely distended by barium the entire shadow, *D*, is made up of the antrum But

proposed, it probably would be an ideal case for a Roux en Y procedure There are, no doubt, a great many adhesions present that will be avoided when the stomach is transected proximal—i e high up proximal to the site of the gastroenterostomy—and the distal limb of the jejunum is brought up over the colon and anastomosed, end to side to the stomach The short jejunal loop just distal to the ligament of Treitz is anastomosed to this distal loop of the jejunum, constituting a Roux-en-Y procedure We have done quite a few of these in instances such as we find this case to be, and if the acid is normal or near normal, we do not hesitate to do it It is not the proper operation to do in a patient with a high acid because the bile is diverted below the site of anastomosis to empty into the distal jejunum, and therefore does not enter the short gastric segment

DR BOCKUS Dr Monaghan, I think, had had an experience with a case somewhat similar

DR MONAGHAN We had a situation very similar as far as the indications for surgery are concerned and we did not know of the communication with the biliary tree previous to operation The surgeon found to his surprise that the gallbladder had been anastomosed to the antrum of the stomach when the original gastroenterostomy had been done The surgeon who performed the original operation apparently felt that with the gastroenterostomy if he anastamosed the gallbladder to the antrum of the stomach so that further neutralization of the stomach content could take place, there was a lesser likelihood of recurrence of ulcer I wish to mention this as a possible explanation for the findings here

DR. BOCKUS Dr Finkelstein, do you believe that such an anastomosis could explain the roentgen findings in our patient?

DR FINKELSTEIN I recall the case that Dr Monaghan showed I would like very much to say that that couldn t be the situation in our case, but frankly I am not sure It is worth noting though that the collection which I have assumed to be in the gallbladder or certainly in an accessory pocket that could be gallbladder is not in close relationship with this pocket way over here

DR. BOCKUS You couldn t say which pocket filled first with barium could you?

DR FINKELSTEIN I don t know I believe that this was not identified fluoroscopically It might be that a reexamination by x ray now that we are familiar with the general problem might make it possible to work out some of these points more definitely I think it would be worth a try I don t know whether it would be critical in deciding on the handling of the case

DR MONAGHAN Do you think the fact that you couldn t visualize the gallbladder by cholecystography would favor a surgically created anastomosis between the gallbladder and the antrum? If the fistulous tract involves only the ducts and the gallbladder fills with barium via the cystic duct why did not the gallbladder fill by cholecystography?

DR BOCKUS Your hypothesis is sound if our roentgen interpretation of the shadows we see is the correct one Dr Hawthorne, was this type of anasto-

and duodenum and of the peculiar linear shadows suggesting barium in a fistulous tract, some thought should be given to spontaneous filling of the biliary tract via the papillae of Vater Prior to 1937, Borman and Rigler collected 16 instances of regurgitation of barium through the *common duct* This is exceedingly rare and probably does not account for the findings in this case

If we could ignore the abnormal communication which exists between the biliary and the upper gastrointestinal tract, we would still be faced with a decision concerning the advisability of operation because of (1) recent massive hemorrhage, (2) presumptive evidence of old duodenal ulcer, (3) stenosis of the duodenal cap and (4) an unphysiologic gastric emptying mechanism (barium leaves the stomach via both the stoma and pylorus) Lysis of the gastroenterostomy and an adequate partial gastrectomy would seem to be the best remedy for this situation In what way should the additional factor of a duodenobiliary fistula modify our decision concerning operation, bearing in mind, of course, the possibility that the biliary communication may actually be with the gastric antrum rather than with the duodenum? The decision concerning the imminent need for surgical treatment would be modified to some extent by the presence of possible gastrojejunal ulcer Is it Dr Finkelstein s opinion that we have no roentgen evidence of an ulcer crater at the stoma?

Dr Finkelstein Yes We have many more exposures here of the anastomosis itself showing the mucosal pattern in approximately that manner and there is no suggestion of an ulcer crater

Dr Bockus Would Dr Hawthorne care to discuss the surgical approach to the problem, bearing in mind both the gastroduodenal situation and the problem presented by the internal biliary fistula?

Dr Hawthorne The difficulty of surgery, of course, will depend a lot upon just what is found out about the fistula It seems to me that if the duodenum is transected, or possibly a transection in the prepyloric region and the prepyloric segment turned in with an excision of the gastric mucosa, then the fistulous tract would cease to be a problem Of course, that is conjecture Now this is the kind of a case in which the duodenum may not be so easily transected, just distal to the pylorus It brings up the question of the advisability of transecting the stomach proximal to the pylorus with a clean dissection of the gastric mucosa down to and including the mucosa of the pylorus and a turning in of the short proximal gastric stump that consists of submucosa, mucosa and serosa This is a technic that Wangensteen developed a few years ago and that has been most successful in our hands in instances where the duodenum is involved in an extensive process that has been so well demonstrated in this case It is very difficult at times to dissect the proximal duodenum free from an involved mass of scar tissue and sinus tract, etc In so doing, one may inadvertently open the duodenum well below the pylorus, and thereby increase the hazard of the operation, due to improper closure of the duodenal stump

One more thing, since this man has a normal acid and if a gastrectomy is

proposed, it probably would be an ideal case for a Roux en-Y procedure There are, no doubt, a great many adhesions present that will be avoided when the stomach is transected proximal—i e high up proximal to the site of the gastroenterostomy—and the distal limb of the jejunum is brought up over the colon and anastomosed end to side to the stomach The short jejunal loop just distal to the ligament of Treitz is anastomosed to this distal loop of the jejunum, constituting a Roux en Y procedure We have done quite a few of these in instances such as we find this case to be, and if the acid is normal or near normal, we do not hesitate to do it It is not the proper operation to do in a patient with a high acid because the bile is diverted below the site of anastomosis to empty into the distal jejunum, and therefore does not enter the short gastric segment

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mosis being done occasionally twenty years ago? You're old enough to remember Did you ever do an operation of this type?

DR HAWTHORNE Yes, for stricture of the common duct

DR BOCKUS I was referring, of course, to a cholecystogastrostomy in the treatment of duodenal ulcer in association with a gastroenterostomy That was being done occasionally?

DR HAWTHORNE I did not do it in association with ulcer, only as a palliative operation in the treatment of obstructive jaundice

DR BOCKUS Some surgeons, however, were doing this double anastomosis for ulcer?



Fig 199 June 16 1947 After evacuation Extensive polypoid changes evident

DR HAWTHORNE Yes One of our very best technical surgeons here in Philadelphia did a great many of these double anastomosis operations years ago

DR BOCKUS It would appear then that serious consideration will need to be given to the possibility of a surgically created anastomosis between the gallbladder and the antrum This patient is in excellent condition He has no hyperbilirubinemia There are no symptoms related to his biliary tract His studies as yet are incomplete We will carry out detailed pancreatic function studies, perhaps subject him to gastroscopy and turn him over to the tender mercies of Dr Finkelstein for further roentgen investigation I apologize for spoiling your day with a case of this type in which a final diagnosis or decision concerning treatment cannot be made today

Dr Willard has a brief case presentation

DR. WILLARD (*Case 2*) S S , a nineteen year old boy, had an attack of dysentery while in the Navy aboard ship off Japan in 1945 This attack was not severe and was of short duration However, there were several recurrences during the next fifteen months consisting of eight to ten bloody stools daily He was hospitalized in February 1947 because of an acute recurrence during which he lost weight from 152 to 96 pounds Improvement occurred gradually and upon discharge in May 1947 he weighed 146 pounds and was having one or two soft stools daily without blood. A barium enema during that admission



Fig 200 November 30 1948 A Filled distal colon. B Distal colon after evacuation. Mucosal pattern mottled but striking improvement in polypoid reaction.

revealed irregular haustrations and narrowing of the distal colon with fuzziness of the outline of this portion of the colon Sigmoidoscopy showed typical active idiopathic' ulcerative colitis

One month after discharge symptoms recurred with five to six bloody stools daily associated with a septic temperature the fever rising to 103 in the evening Sigmoidoscopy revealed diffuse ulcerative colitis with irregular areas of complete mucosal denudation Repeated studies failed to demonstrate ameba or cysts but he was given courses of emetine and carbarsone in spite of the negative findings Smears were negative for tuberculosis and the chest x-ray was negative The sedimentation rate was 75 mm. in one hour but the

blood count was within normal limits A barium enema in June revealed a narrow rigid colon from rectum to cecum with abnormal mucosal pattern throughout indicative of polyposis (Fig 199) The ileum was not involved.

Clinical improvement was slow but the sigmoidoscopic picture changed during the next month There was less diffuse involvement and the large excoriated areas showed evidence of granulation and healing Associated with this change, the polyposis became more marked In August there was rapid clinical improvement with progressive weight gain and reduction in the number of stools to four or five soft evacuations daily

By September 1947 the patient had regained 20 pounds and was feeling quite well although the sedimentation rate remained elevated (38 mm in one hour) and his stools were not formed X-ray showed evidence of polyposis

Improvement continued and in November 1947 the sedimentation rate was 3 mm in one hour, the weight 154 pounds (low 120) and the bowel movements cut to one or two formed stools daily Barium enema now revealed more flexibility of the colon but with little change in the polyposis By sigmoidoscopy the mucosa was less congested, the irregular ulcers largely healed and the polyps smaller and less turgid Biopsies on several occasions were reported as showing no evidence of malignant change

Subsequent x ray studies were made in April and November 1948 (Fig 200) On the latter examination, evidence of polyposis was decidedly less marked, in fact the mucosal pattern was seen to be fairly normal except for some mottling in the descending and pelvic portions Sigmoidoscopically the large ulcers were healed and the polyps appeared as small shreds of mucosa, some forming narrow bridges across part of the lumen of the bowel

This case is presented because of the marked regression of reactive polyposis associated with chronic ulcerative colitis I have not observed such a case previously

We have been concerned about the possibility of malignant change in such cases and have advised colectomy in this case, but the patient decided to take his chances without surgery at this time

Dr Bockus Do you wish some argument?

Dr Willard Yes sir

Dr Bockus Have the polyps disappeared or not?

Dr Willard They have certainly undergone marked regression

Dr Monaghan In the etiology of this case was there any specific organism involved, did you say?

Dr Willard No, none was proved

Dr Monaghan You thought that this was an instance of ordinary non specific ulcerative colitis?

Dr Willard As far as could be determined, it was

Dr. Finkelstein Some abnormality of the mucosal pattern is suggested throughout, here in the hepatic flexure area the mucosal pattern has a somewhat cobblestone configuration, but one does not see the larger polypoid lesions that were suggested in earlier studies, so I would say that a polypoid change is still present but it is undergoing progressive regression

DR MONAGHAN This is interesting in the sense that, of course, at one time polyposis was used as one of the definite indications for colectomy in ulcerative colitis There have been many cases of this nature I think one of the best ones that we have observed is in Dr Bockus book That patient had ulcerative colitis for quite some time undiagnosed before she came under treatment, and at the time that she was first studied she had a very extensive polyposis The polyps varied in size and shape and many of them were biopsied With treatment the polyps sigmoidoscopically completely disappeared and there was a return to a normal membrane which may have been somewhat atrophic The last film that was reproduced in the book showed a few polyps here and there with a great increase in the distensibility of the colon The polyps have since disappeared This girl has had no recurrence of her ulcerative colitis despite the fact that she s probably going to die from her pulmonary disease She has multiple abscesses in the bases of her lungs from a very severe chronic bronchiectasis I don t think that change in polyps of this nature is uncommon I suspect that many of the instances of polyposis that persist are actually examples of adenomatosis with secondary colitis We have seen several cases of this type

DR BOCKUS How many patients have you had with ulcerative colitis complicated by polyposis in which the polyps have disappeared and a recurrence has not occurred within five years?

DR MONAGHAN Any recurrence of ulcerative colitis? The case mentioned is the only one that I can remember distinctly I believe there may have been several others

DR BOCKUS I think there can be no doubt about the regression of polypoid change in some patients Evidently I am not quite so optimistic about the ultimate result in cases with polyposis My feeling has been that usually they don t entirely disappear and most patients with this degree of polyposis have recurrences and get into real difficulties

DR TUMEN (*Case 3*) The patient I brought in for discussion is a man whom I have known medically for about eight years I saw him originally in 1940 at age fifty-six At that time he was referred because he had diarrhea of about three months duration and the studies which were carried out then showed the presence of a defect in his sigmoid which at the time of the initial examination was supposed to have been a malignancy He had what seemed to be an infiltrating lesion of the sigmoid However, he also had a great many diverticula and after a short period of observation it was determined that what he probably had was diverticulitis and on a conservative program he was rendered symptom free Unfortunately, I do not have the films of that period

Subsequent films following this initial bout in 1940 showed a recession of the previously present filling defect in his sigmoid, a decrease, to a very large extent in the irritability of his colon and marked general improvement I saw the man at relatively long intervals during the periods between 1943 and June 1948 He came back occasionally not because of much in the way of bowel symptoms but for the usual follow up examination and the last films taken prior to the set which Dr Finkelstein will show in a few minutes were taken

in 1944 and showed the ordinary type of diverticulosis of the bowel with a little irritability and that was all

In June 1948 he complained of a recurrence of diarrhea but because of illness of his wife, he did not have any studies carried out Then between June and October he became rather ill, began to lose weight, became quite cachectic and returned in October because of a recurrence of his diarrhea, pain in the left lower abdomen, the loss of about 15 pounds in weight and, something which troubled him a great deal, a nodular type of eruption over his lower legs and particularly a nodule behind his left ear, which had all the dermatologic characteristics of erythema nodosum, but which was extremely painful His studies at that time showed a moderate anemia and were essen



Fig 201 Constricting lesion of sigmoid resembling neoplasm in association with diverticulosis (October 8 1948)

tially negative otherwise from a laboratory standpoint His sigmoidoscopic examination was entirely negative He did have stools that were positive for occult blood and at that time the first set of films, which Dr Finkelstein has here, were taken Those were the ones of October 8 and 11, 1948, and they show a defect in his sigmoid which was a cause for concern (Figs 201, 202)

Dr Finkelstein This is the first time I've seen these films I think you can see the nature of the defect in the mid sigmoid—a somewhat elongated area of moderate constriction, in association with evidence of diverticulosis The arrow on Fig 202, whether accidentally or otherwise, is pointing to a local faint collection of barium, smooth in outline which has a configuration of a large diverticulum This configuration, of course, could be due to either a colonic neoplasm or an inflammatory lesion such as a diverticulitis In my

experience, at least, I have been so consistently wrong in guessing which of the two possibilities is more likely in a given case, I doubt if a guess would be of much value



Fig 202 Same as Fig 201 three days later



Fig 203 Same patient as Fig 201 three weeks later Suggestive of increasing obstruction

DR TUMEN When I encounter this situation my feeling is that the burden of proof is on the person who says it is not malignant The patient was treated medically for a period of about three weeks and then an additional film was taken on the first of November (Fig 203) The x ray man who did these

studies commented on the difficulty which he had in getting barium past the involved area of the sigmoid, and he considered that a moderate degree of obstruction was present at that time Since it was impossible to be certain of the diagnosis, and also because the patient had continued to be quite ill and was having major symptoms, an operation was advised While the patient was trying to make up his mind he developed an acute colonic obstruction on November 6 Obstipation had been present for close to forty eight hours I found an acutely distended abdomen, all of the physical and roentgenographic signs of obstruction were present He was operated upon initially by a cecostomy to relieve the acute distention of the colon The surgeon was able to slip his finger over to the left side and feel an infiltrating freely movable lesion, in his opinion probably inflammatory A few days later, after the cecostomy had relieved the distention and the patient had been restored to normal fluid balance, the surgeon went back and did a resection and took out an inflammatory mass which evidently had undergone a great deal of fibrosis as a result of repeated attacks of diverticulitis This man had no neoplasm, but a very fibrotic area secondary to multiple attacks of diverticulitis with almost no lumen left in the bowel at the time that the section was taken out

Dr Bockus The lesson is what?

Dr Tumen There are several In my experience a diverticulitis going on to complete obstruction of the colon is extremely rare The other lesson, of course, is that of x-ray interpretation Although the roentgenologist who had done these studies felt as Dr Finkelstein did that the changes were probably due to inflammatory lesions, the diagnosis had to wait for surgery in order to be definitely established

Another point, probably not of great importance in this particular discussion, but one which I have observed a few times during the past year or two, is the fact that this patient had erythema nodosum I have seen in the last year four patients with colonic lesions who have had erythema nodosum which cleared up after the colonic lesion was removed What has your experience been in this regard?

Dr Bockus Do you mean the occurrence of erythema nodosum in association with colonic neoplasm?

Dr Tumen No, this patient did not have a neoplasm

Dr Bockus The other three?

Dr Tumen Two of them were instances of carcinoma, one was a case of severe ulcerative colitis and with the subsidence of the colitis the erythema nodosum disappeared In this patient, when his inflammatory lesion was removed, the erythema nodosum disappeared almost instantaneously In the other two patients who had colonic cancers resected, the erythema nodosum disappeared very promptly I wonder what your experience has been?

Dr Bockus As far as colonic neoplasms are concerned I do not recall the associated occurrence of erythema nodosum The last few instances of erythema nodosum that I have seen in intestinal disease were in patients with ileocolitis and ulcerative colitis

DR TUMEN I have encountered erythema nodosum in association with ulcerative colitis a number of times but it so happens that in very rapid succession I saw these patients with massive lesions of the colon and erythema nodosum the latter clearing rapidly with treatment of the colonic lesions

DR BOCKUS This case of Dr Tumen's brings to mind several items worthy of comment First, the difficulty presented by the differential diagnosis of diverticulitis and carcinoma Some years ago my clinical experience seemed to bear out the conclusions of certain statistical papers presented at that time It was my impression that carcinoma was not commonly encountered in a segment of colon involved in diverticulosis In recent years we have had to change our views in this matter During the last several years we have presented quite a few patients with carcinoma and diverticulosis in the same segment of the bowel usually the sigmoid Often it is exceedingly difficult to exclude the presence of carcinoma of the sigmoid in an area involved in diverticulitis, acute or chronic With the most expert roentgen study often repeating the examination several times, the opinion concerning the presence or absence of cancer is usually correct In some instances it is impossible to be sure The questionable lesion is almost always beyond the reach of the sigmoidoscope and other clinical aids may prove of little help In these questionable cases the choice must be made between conservative treatment with frequent follow up roentgen studies and exploration At times in late life the operative risk may be such that a conservative policy is adopted Usually when the chance of carcinoma seems greater operation is advised Unfortunately, at operation the differential diagnosis cannot be clearly established and a colostomy is decided upon as a temporary expedient, followed by a cooling-off period After six to eight weeks reoperation will usually be possible and definitive surgery performed if necessary Frozen section at the time of first operation is not a very reliable procedure In these questionable cases, often there is a great deal of inflammatory reaction of the involved segment, obscuring the carcinoma if one is present

Dr Tumen has asked about the frequency of occurrence of temporary complete obstruction in association with diverticulitis Transient complete obstruction certainly is not common, but it does occur In most instances the complete obstruction is overcome within twenty four to forty eight hours by rest, sedation, nothing by mouth and parenteral nourishment Ordinarily emergency operation is not required

DR BOCKUS May we hear from the surgeon?

DR HAWTHORNE We do not like to take frozen sections in lesions of the type under discussion One may get into all sorts of trouble There is such a marked inflammatory reaction around what might be the site of the tumor that if you did take sections of that inflammatory tissue, it would not show any tumor tissue In order to go in deep enough to get a proper section you may find that you are in the lumen of the bowel and then you have difficulty that is attendant to that It is very difficult, often, even with the lesion in your hand to try and decide what you're dealing with so that, after once having opened the abdomen we proceed with the resection and as Dr Bockus has

said, the operation isn't at all easy because so often the entire descending colon may be involved It may be necessary to do a very radical procedure and remove a great deal of colon in order to find tissue that is safe enough to anastomose Ordinarily what we like to do in a lesion of this type is to free it and lift it out as a Mikulicz procedure, it is safer than attempting an end to-end anastomosis because the tissues are usually edematous and suturing is not entirely safe

DR BOCKUS You usually do a colostomy first, don't you?

DR HAWTHORNE Yes, a complementary colostomy is often performed, particularly if a partial obstruction has been present

Chronic Non-specific Enteritis and Entero-Colitis

ETIOLOGY AND CLASSIFICATION OF TYPES

THOMAS A JOHNSON, M D

When Crohn, Ginsberg and Oppenheimer first called attention to this entity in 1932, the name they had in mind was *terminal ileitis*, referring to the fact that the involvement was in the lowermost portion of the ileum immediately adjacent to the cecum

Crohn originally stated that this type of involvement of the terminal ileum was in itself a distinct clinical entity Later the term *regional ileitis* was coined, having reference to the fact that the disease involved portions of the ileum other than the terminal ileum and that *skip areas* might be present

As more observations began to be reported it was found that the term regional ileitis was not adequate, since the entire mesenteric small intestine was found to be involved to some extent in other instances The term *jejuno-ileitis* or *ileo jejunitis* has been applied to a small group of cases with this diffuse involvement of the jejunum and the ileum

Crohn originally stated that the disease stopped sharply at the ileocecal valve and did not involve the cecum Subsequent observations showed that in many instances the disease did pass over into the cecum hence the term, *ileocolitis* The involvement in the colon may not be a continuation of the ileal involvement but may occur as one or more areas of disease of segments of varying length with skip areas between Ileocolitis must be differentiated from right sided colitis a variety of ulcerative colitis Distal ulcerative colitis located initially in the rectum and progressing in a retrograde manner to the cecum may in some instances, extend into the ileum

The literature on cicatricial enteritis may seem confusing unless one keeps in mind the various types of involvement The term cicatrizing enteritis might well be applied to the entire group Chronic non specific granuloma of the small bowel while not recognized as an entity at least was recognized as a disorder many years before Crohn first called attention to regional ileitis To Crohn belongs the credit for focusing our attention on this important entity

We recognize acute and chronic ileitis Acute ileitis usually causes lower right quadrant distress that cannot be differentiated clinically from acute appendicitis The true nature of the condition is recognized at the time of operation Acute ileitis may resolve spontaneously with no apparent residual Opinion varies as to whether or not chronic ileitis is a sequel of the acute form Many believe that chronic ileitis bears no relation to acute ileitis Apparently some cases of acute regional ileitis represent the initial phase of stenosing ileitis

X RAY EXAMINATION TECHNIC AND RELIABILITY

The small intestine can usually be examined satisfactorily by observing the progress of a barium water meal through it The aim of this examination is to visualize the contour, distensibility, mucosal pattern and mobility of every loop individually This involves both careful fluoroscopy and film studies Since the rate with which the barium leaves the stomach and passes through the small intestines varies in different individuals a rigidly routine method of examination often is inadequate

One popular procedure consists in the exposure of a large film of the abdomen at hourly intervals after the barium meal inspection of the wet films, and fluoroscopy only if something abnormal is discovered in the films Since some intestinal loops are almost always superimposed on each other, they cannot thus be individually seen without proper compression applied to separate them under fluoroscopic guidance Frequently motility is quite rapid requiring fluoroscopic and film examination every fifteen to thirty minutes, the most valuable time for observation occurring during the first sixty or ninety minutes Occasionally, when adequate filling of a suspicious loop cannot be achieved in this manner, more complete distention might be obtained by small intestinal enema or by the barium saline and ice water rapid technic of Weintraub and Williams

The exposure of adequate films with and without compression is essential, since inconspicuous lesions are readily overlooked fluoroscopically, and even when obvious disease has been seen fluoroscopically its finer details such as small fistulas are best identified in films Also the radiographs comprise a permanent record for future comparison, permitting estimation of the rate of progression of the pathologic process and at times providing an objective basis for prognosis

In addition to compression, certain other technical tricks may be attempted, particularly in attacking the common problem of separating pelvic loops of ileum The use of an exaggerated Trendelenburg position tilting the head of the fluoroscopic table downward 60 to 80 degrees, seems the easiest way to accomplish this, particularly when upward displacement of the pelvic loops is augmented by applying a plastic or balsa wood bulbous compression paddle (Fig 204) Tilting the head of the table downward 15 or 20 degrees is usually of no value

Another maneuver making deep pelvic loops of ileum accessible is to give the previously fasting patient two glassfuls of water to drink The resultant distention of the urinary bladder may push the ileal loops upward sufficiently to permit individual inspection (Fig 205) Distending the rectosigmoid by a plain water enema may have a similar effect The routine use of oblique and lateral projections for this purpose is taken for granted

The barium enema must be performed with similar care Adequate preparatory cleansing by laxative and enema is essential in order to obtain good visualization of the mucosal pattern and in order to eliminate gas and feces which might simulate polypoid changes or granulomatous masses The aim of the examination is to visualize and record every part of the colon The use

The gross and histologic character of cicatrizing enteritis is well known and will not be described at this time One of the features in many cases is the formation of fistulas, either external or internal Internal fistulas occur between loops of the small or large bowel and in some instances may extend to adjacent organs such as the ureter, uterus or urinary bladder

Crohn believes that many perirectal fistulas have their origin in cicatricial enteritis Any patient who presents with a perirectal fistula should be studied from the point of view of a possible cicatricial enteritis An external fistula commonly occurs through the abdominal scar following removal of an acute appendix, from a patient with terminal ileitis

The etiology of cicatricial enteritis is unknown It certainly is not tuberculosis In no authentic instance has there been recorded any evidence of tuberculosis Some investigators have postulated that an unrecognized chronic bacillary dysentery may play a role in the etiology of this disease This is an interesting speculation for which we have no proof Some experimental work was reported some years ago by Richert and Mathews in California, in which attempts to reproduce this disease were successful in instances in which the lymphatics in the mesentery were blocked by sclerosing substances The lesions were more striking if bacterial organisms were injected intravenously at the same time I believe that the initial lesion of cicatricial enteritis occurs in the mucosa of the bowel Secondarily, there ensues a blocking of the regional lymphatics with subsequent further alteration in the structure of the bowel wall

There are many people who believe that cicatricial enteritis and ulcerative colitis, both of unknown etiology, have many things in common, and in late *stages may be difficult to differentiate, both representing variants of a common* etiologic factor Clinically, both diseases present characteristic patterns in typical cases, however, in instances with complete colonic involvement including the terminal ileum it is difficult to state with certainty that we are dealing with separate entities Perhaps it should be stated, however, that when the colon becomes involved in association with stenosing enteritis, the rectum and low *sigmoid are almost invariably spared*

ROENTGEN FEATURES

ARTHUR FINKELSTEIN, M D

It is my purpose to discuss some of the interesting roentgen manifestations of non-specific enteritis and entero-colitis Even after excluding those forms of colitis which are not associated with small intestinal involvement, the subject is too large to permit an adequate systematic review *The present* remarks will therefore be restricted to special aspects which have been particularly puzzling or revealing to us



Fig 205 When pelvic loops of ileum are too deep to permit separation by palpation A they may be displaced upward and become palpable after the patient drinks water and distends the bladder B

Fig 206 Occasionally misleading configuration of terminal ileum simulating ileitis when filled by reflux during barium enema A and B Progress meal two days later demonstrates a normal terminal ileum C and D





Fig 204 Multiple segments of regional non specific enteritis are present with dilated skip areas between them The extent of the lesion is not clearly observed in the usual prone exposure A In an exaggerated Trendelenburg position augmented by compression the obscuring loops are displaced cephalad B

A few recent experiences have cast doubt on the reliability of negative x ray findings in patients with symptoms of ileitis Figure 207 shows the appearance of the terminal ileum during successive stages of a progress meal The contour, caliber marginal outline, peristaltic activity and mucosal pattern are normal Yet this patient had been operated upon only a few weeks before the x ray examination, and a definite terminal ileitis had been found It was a rather acute terminal ileitis, and was not resected One might object that the radiographic findings were negative because the disease was too recent However, I have recently seen a terminal ileum which appeared quite normal on detailed x ray examination made sixteen months after operation (*without resection*) in which typical chronic terminal ileitis was found associated with the usual mesenteric thickening, enlarged mesenteric lymph nodes, etc The first x ray examination was made elsewhere six or eight weeks postoperatively and it was also negative These two cases may very well be exceptional but they are certainly disquieting

Contrariwise in postoperative reexamination after resection x ray evidence of recurrence usually long precedes symptoms in our experience This will be referred to later

X RAY APPEARANCE—SMALL INTESTINE ONLY

STENOSING TYPES

From the standpoint of gross roentgen appearance the stenosing types of non specific inflammations of the small intestines may be grouped as (1) terminal (2) regional nonterminal, (3) multiple, with intervening normal skip areas

Stenosing terminal ileitis is usually easily recognized by x ray examination Figure 208 illustrates this condition showing a narrowed stiff segment of terminal ileum in which the mucosal pattern is slightly distorted—approximately 5 cm in length as shown by barium enema, (Fig 208, *A*) The progress meal study, one week later, gives a better indication of the degree of narrowing under more nearly physiologic circumstances (Fig 208 *B*)

Of course, the involvement of the terminal ileum may be merely a part of a long continuous segment of regional enteritis Fig 209, in which the disease extends for a distance of several feet In addition to the narrowing blurring of mucosal pattern and slight nodularity of the mucosal pattern in places, one also notes a certain fixity of contour indicative of stiffening, and separation of adjacent loops which can be attributed to mesenteric thickening

Early in our experience with ileitis we were confused when a segment of small intestine presented the typical configuration of stenosing enteritis at most periods of observation as in Fig 210 *A* but on infrequent occasions became briefly distended to normal caliber as a large bolus of barium passed through it as in Fig 210 *B* This occasional distensibility is difficult to explain when marked stenosis is found at operation That the segment is really diseased is definitely indicated by the mucosal distortion, fixity of contour (stiffness) slight marginal raggedness, and by a clear zone separating it

of oblique and lateral projections, compression of accessible areas, the erect position, the exaggerated Trendelenburg position and the frequent use of double contrast by injecting air, are all valuable and commonly permit demonstration of lesions which are otherwise not detected

When clinically a lesion is suspected in the ileocecal area, examination by barium enema alone is not adequate even when the terminal and distal portions of the ileum are visualized by reflux Even if disease is thus demonstrated in the terminal ileum, it is quite possible that some distance higher

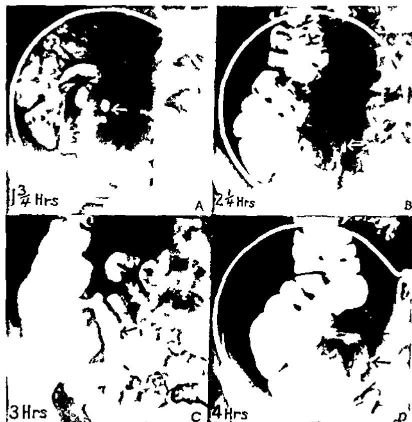


Fig 207 Normal roentgen appearance of terminal ileum several weeks after operation in which terminal ileitis was found but not resected

in the small bowel there may be another lesion which is much more important because its stenosis indicates impending obstruction, or because it is the site of an internal fistula A similar problem is shown in Fig 206, *A* and *B*, in which barium enema provided reflux filling of the terminal ileum which presented a narrowed and stiff configuration associated with loss of mucosal pattern A tentative diagnosis of terminal ileitis was offered but further investigation by progress meal was recommended before giving a final opinion A progress meal examination two days later revealed an entirely normal terminal ileum, Fig 206, *C* and *D*

Fig 209 Stenosing terminal ileitis continuous with a long segment of distal ileitis The separation between the diseased loops is due to mesenteric thickening Compare with Fig 221



A B

Fig 210 It is surprising that stenosing terminal ileitis may exhibit a very narrow lumen through most of a progress meal as in A but may momentarily distend to a normal caliber as in B

from adjacent small intestines due to pressure upon them by the very thick mesentery of the diseased segment

A regional or segmental area of stenosing enteritis, not situated in the terminal ileum, is not uncommon If it is not producing significant obstruction or if it is deep in the pelvis where overlying loops obscure it, such a segment may be overlooked unless one strives to follow a policy of attempting to visualize every portion of the small intestines, Fig 211, *C* and Fig 204

The latter two cases also illustrate the third type of enteritis, consisting of multiple diseased segments with intervening normal ('skip) areas Such



Fig 208 Stenosing terminal ileitis showing narrowing and stiffness associated with slight mucosal distortion as seen during a barium enema row A When visualized by progress meal one week later the degree of stenosis is more evident row B

skip areas may become quite dilated due to obstruction if they lie between very stenotic segments, as in Fig 204

NON STENOSING TYPE

Of far more interest, because of the difficulty in their early diagnosis, are those instances of non-stenosing non specific enteritis We have been able to recognize only a few of such cases, one of which is shown by Fig 211 At the time of our first examination when she was ten years old, this girl presented a long segment of jejunum which gave a normal roentgen appearance except that the mucosal pattern was finely nodular resulting in a somewhat polypoid or reticular pattern where only a slight mucosal covering of barium was

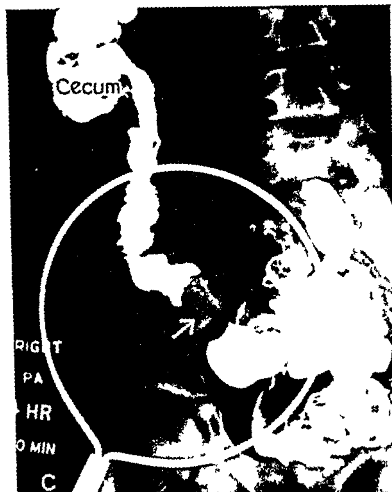


Fig 211 The first examinat on in September 1943 shows a nodular jejunal mucosal pattern without stenosis A Eighteen months later, B, these loops present the typical appearance of segmental enteritis When the compression paddle displaces overlying intestines a short stenotic segment of distal ileitis is now seen, C

present (Fig 211, *A*) When well filled with barium the mucosal pattern of these loops is not seen and the configuration seems normal It is worth noting that the affected loops do not present segmentary narrowing or dilatation nor do they exhibit the broadening of the transverse folds such as might occur in a nutritional deficiency state or in any of the conditions which may be grouped as "motor dysfunctions"

On reexamination eighteen months later (Fig 211, *B*) the same jejunal loops exhibited moderate narrowing irregular marginal outline, a stiff con figuration and these loops are separated from each other because of thickening of their mesentery Instead of the fine nodularity previously described as the mucosal pattern, there is now extensive loss of mucosal pattern interposed



Fig 211 See facing page for legend

X RAY APPEARANCE—ENTERO COLITIS

Simultaneous involvement of the colon and small intestine in a non specific inflammatory process (entero-colitis) may be divided into three major types depending on the side of the lesions and whether or not they are stenotic Whether or not such a classification will serve a useful purpose is a moot question Perhaps such a grouping as the following may at least lead to recognition of differences in behavior of the several types 1 Right-sided colitis or diffuse colitis, with continuous involvement of a *stenotic* terminal ileitis 2 Right sided colitis associated with a *dilated*, stiff terminal ileum 3 Regional or segmental colitis associated with but not continuous with a regional enteritis

Figure 213 *A* reveals a typical right sided colitis (decrease in size loss of haustrations granular mucosa) associated with marked narrowing of the

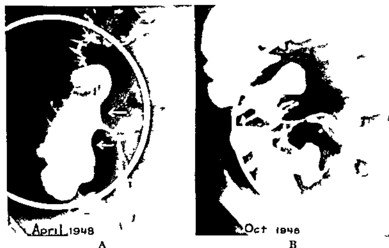


Fig 213 A stenotic terminal ileitis in association with right sided colitis Arrows indicate biconcave impression by thickened mesentery on the medial aspect of the cecocolic juncture B eighteen months earlier when the terminal ileum was less stenotic and there was no definite evidence of colitis

terminal ileum in which the mucosal pattern is extensively destroyed Attention is called to a smooth symmetrical concavity of the medial aspect of the cecum and proximal ascending colon, above and below the entrance of the terminal ileum A similar concavity is noted on reviewing a film of the same patient made eighteen months earlier *B* when there was considerably less stenosis of the terminal ileum and no definite roentgen evidence of colitis This biconcave configuration of the medial aspect of the cecocolic juncture is due to extrinsic pressure by the thickened mesentery It is not present in every case and is probably not pathognomonic, but it is of diagnostic value when other signs are equivocal In our experience the concavity is seen more often in this type of entero colitis than in terminal ileitis alone It is usually visualized best in exposures made with compression, as in Fig 213, *A* and *B*

with occasional inconspicuous larger polypoid defects Obviously the disease process is now changing to the more familiar stenosing type of regional enteritis Attention must also be called to an isolated markedly stenotic short segment of distal ileitis which is beginning to produce obstruction as indicated by slight dilatation of the ileum proximally (Fig 211, C) The discovery of this stenotic segment was of importance in prognosis, since the child could be kept under closer surveillance and the parents warned of impending obstruction which would require operation Were it not for our policy of routinely attempting to visualize every part of the small intestines, the latter lesion would have been overlooked

Another example of extensive enteritis, chiefly of the non-stenosing type, is presented by a young woman, aged nineteen, Fig 212 The pathologic changes are first visible in the distal jejunum where the mucosal pattern is

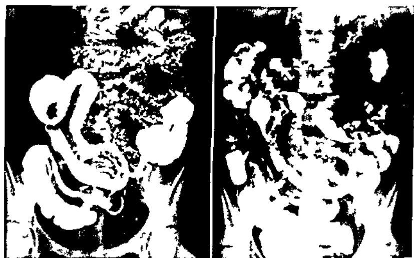


Fig 212 Long segments of enteritis chiefly of the non stenosing type The nodular mucosal pattern helps distinguish it from motor dysfunction patterns

becoming nodular There is no narrowing in this area, in fact some of these loops are slightly dilated In the ileum it is evident that stenosis is beginning to appear Most of the loops present long segments that are straighter than usual, indicating stiffening, the loops are separated from each other due to mesenteric thickening Recognition of these features should prevent confusion with a nutritional deficiency *pattern or a motor dysfunction* The peculiar and striking nodularity of the mucosal pattern is an important criterion for making this differentiation

As yet we do not know enough about the development of non-specific enteritis to make a general statement, but the cases illustrated in Figs 211 and 212 indicate that at least sometimes it begins without stenosis, and later becomes stenotic Our experience in observing the development of post operative recurrences has shown a similar sequence of events, which also suggests that these are the usual stages in the progress of enteritis

consists of isolated nonspecific inflammatory segments of small intestine and of colon, not in continuous relationship with each other. They present the same roentgen appearance as when each occurs alone and are not illustrated here.

COMPLICATIONS

The complications of entero-colitis most frequently identified radiologically are obstruction, perforation and fistulas, adhesions, secondary nutritional deficiency, polypoid mucosal changes and rarely malignancy.



Fig. 215. There is a long segment of terminal ileitis producing partial obstruction. The moderately dilated and stiffened long portion of proximal ileum simulates colitic involvement of sigmoid.

Obstruction is a fairly common complication and may occur either in the small intestines or colon due to progressive scarring and inflammatory swelling of the wall, sometimes precipitated by local perforation and adhesions. In Fig. 215 one sees a long segment of stenotic terminal and distal ileum extending upward from the deep pelvic area and entering the colon anomalously on its lateral aspect. The obstruction produced by this stenosis has been sufficient to cause moderate dilatation in a stiffened loop of ileum proximal to it, which arches out of the pelvis in such a manner as to simulate a redundant sigmoid. Its mucosal pattern is coarsely nodular. The ileum proximal to the arched segment is also dilated to such an extent that these portions of the ileum resemble the distal descending colon and sigmoid.

In Fig 214, *A*, one sees an example of colitis of the entire colon, somewhat more advanced on the right where the cecum has shrunk to such an extent that it is barely identified Because of the wide dilatation of the ileocecal juncture and of the terminal ileum, it is at first difficult to distinguish the colon from the adjacent ileum As in the other few examples of this type of lesion which we have encountered, in the present case also the anatomic relationship of ileum to colon is demonstrated best by double contrast enema, Fig 214, *B* The latter also clearly shows the nodular mucosal pattern of the terminal and distal ileum identical with that of the right colon A small irregular streak of barium projecting downward from the cecum might be either the fibrotic remnant of the cecum or, more likely, the appendix



Fig 214 A generalized ulcerative colitis, more advanced on the right associated with a dilated terminal ileum B close up of the ileocecal area after double contrast enema shows the same type of inflammatory changes in the dilated terminal ileum

We do not know why some patients have a dilated terminal ileum and others a stenotic terminal ileum, in association with right sided colitis In a few instances of generalized and right sided colitis we have observed incompetency of the ileocecal valve, slight dilatation and stiffening (fixed contour) of the terminal ileum associated with a questionably granular mucosal pattern The gross findings at operation have been variable, at times slight inflammatory changes were recognized in the terminal ileum similar to the process in the colon, and in other cases no gross pathologic changes were identified These patients have not been followed long enough to know whether they would eventuate in forms such as Fig 214 We suspect, however, that in such cases as the latter, the disease started primarily in the colon and the terminal ileum became secondarily implicated

The third type of simultaneous involvement of the small intestine and colon

until late in the examination, Fig 216, *B*, and was almost overlooked because of the more striking but secondary nutritional changes throughout most of the small intestines

Although granular or slightly nodular polypoid changes are often noted in the mucosa of the small intestine the really significant post inflammatory polyps arise in the colon Their recognition usually depends on visualization of the mucosal pattern which is generally accomplished best by double con



Fig 217 Extensive postoperative recurrence of enteritis in the most distal ileum following resection of terminal ileum and establishment of an ileo proximal ascending colostomy

trast enema Rarely carcinoma supervenes presumably superimposed on such earlier polypoid changes

POSTOPERATIVE RECURRENCES

We have made routine follow up x ray examinations of all of our patients who have had resections because of non-specific entero colitis or enteritis alone A high incidence of recurrences has been found sooner or later These recurrences are usually recognizable radiologically long before the patient presents symptoms The importance of repeated careful postoperative roentgen examinations is therefore obvious if one attempts to evaluate dif-

The patient's symptoms were chiefly due to obstruction which ultimately required resection The dilated arched loop was proved to be involved by ileitis

When a free perforation into the peritoneal cavity occurs, the roentgen findings are the same as in perforation from other causes There may be evidence of free air in the peritoneal cavity and later there may be demonstrable signs of peritonitis If localized perforation occurs and if it is detected in survey films, the appearance will be indistinguishable from the findings in local perforation due to other causes

More often the perforations are local, and occur between adjacent loops of small intestine resulting in fistulous communications between them, or they may occur between the small intestines and any part of the colon When such fistulas occur there is likely to be some local peritoneal soiling with resultant



Fig 216 Small intestinal pattern consistent with a nutritional deficiency state or non tropical sprue A The underlying basic pathology is terminal ileitis with multiple fistulas shown in close up B

fixation of loops to each other or to the parietal wall, which may be identified by careful palpation during fluoroscopic examination Such fistulas are not likely to be demonstrated unless one follows a routine policy of attempting to visualize each intestinal segment in its entirety In Fig 216, *A*, one sees an example of a progress meal study of a young woman whose outstanding clinical findings were malnutrition and steatorrhea Throughout most of the x ray examination *the small intestinal pattern was that of a nutritional deficiency state* A peculiar flocculent or granular distribution of the barium, seen best in close up in Fig 216, *B*, suggested non tropical sprue or steatorrhea in other cases of which we have seen similar small intestinal hypomotility, dilatation, and granular or flocculent distribution of the barium In the present case the fact that the fundamental cause of the patient s difficulties was a distal ileitis with multiple fistulas between ileal loops was not recognized

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ferent types of therapy, but particularly various surgical procedures It is necessary to consider the situation analogous to malignancy, requiring regular x-ray reexaminations over a period of five to ten years before the efficacy of any particular form of treatment can be adequately estimated

Since certain deformities may be produced by the surgical procedure itself, it is extremely valuable to perform the first x ray examination within a few weeks after operation in order to establish a base line configuration for future comparison In order to avoid slip-ups, it is a useful policy to make the first



Fig 218 Recurrence of ileitis adjacent to the anastomosis with the midtransverse colon detected two and a half years postoperatively Same patient as *Fig 215*

roentgen study before the patient is discharged from the hospital post operatively

Figure 217 indicates an extensive postoperative recurrence at the time of our first x-ray examination which was performed after the patient's diseased terminal ileum had been excised elsewhere and the distal ileum anastomosed to the proximal ascending colon *She was reoperated, the distal ileum and* right colon were removed and an ileo-transverse colostomy performed A recent x ray study shows a long segment of another recurrence, again in volving the most distal remaining portion of the ileum The patient remains almost completely symptom free

The patient whose long segment of terminal and distal ileitis was shown in Fig 215 was subsequently operated upon The distal ileum cecum ascending colon and hepatic flexure were removed A side to side anastomosis of the remaining ileum to the midtransverse colon was made leaving long blind ends of ileum and distal transverse colon which occupy the right upper abdomen in the progress meal study made two and a half years postoperatively (Fig 218) A segmental recurrence is evident (arrow) in the ileum immediately distal to the anastomosis

A man presenting a long segment of distal (but not terminal) ileitis was operated upon The distal and terminal ileum along with the right colon were resected and an ileomidtransverse colostomy was established His first post operative x ray examination made before he was discharged from the hospital shows normal distal ileal loops, Fig 219 *A* Reexamination fifteen months later discloses definite recurrence in a distal segment of ileum, but not the



Fig 219 A normal appearance of distal ileal loops immediately postoperatively following resection of distal (not terminal) ileitis The anastomosis is indicated by X The arrow indicates the normal appearance of the site of future recurrence Reexamination nine months later was also negative B examination fifteen months after operation shows recurrence (arrow) in a distal but not most terminal ileal segment

most terminal portion of remaining ileum It will be recalled that his original ileitis also implicated the distal ileum but not its most terminal portion

This tendency for recurrences to mimic the original lesions has not occurred invariably, and may not be borne out by a longer experience Nevertheless it is challenging since in some obscure way it seems to give some hint the significance of which we are not yet able to grasp, concerning the pathogenesis of these lesions

DIFFERENTIAL DIAGNOSIS

In infants and children not infrequently one visualizes a peculiar finely nodular mucosal pattern in the terminal ileum which presents no other abnormality (Fig 220) We have observed this appearance occasionally during the past few years and at first feared that it might represent a non-stenotic phase of regional enteritis, similar to Fig 211 and Fig 212

But we have not been able to correlate it with the patient s symptoms The subsequent course of these patients did not suggest any small intestinal lesion Although we did not understand the cause of this mucosal nodularity, we felt that it was not of clinical significance Recently Dr Wells of Presbyterian Hospital, New York, has demonstrated that the configuration is due to prominent lymph follicles of the terminal ileum, and is apparently not significant

In Fig 221 one observes multiple short segments of narrowing, areas in which the mucosal pattern is slightly nodular, fixity of contour, separation



Fig 220 Nodular mucosal pattern of the terminal ileum of a child Evidently due to prominent lymph follicles and probably not of clinical significance

between loops suggesting mesenteric thickening slight dilatation as in skip areas between the narrow zones In brief, this is the configuration of regional non-specific enteritis The case is presented by courtesy of Dr J Edward Berk who informed me that at operation the patient was found to have an extensive lymphosarcoma of the ileum From the roentgen standpoint I do not know how to distinguish such an appearance from certain types of enteritis, as Fig 222 If on routine x ray examination of the chest one finds evidence of metastasis, or if physical examination discloses lymphadenopathy, the true nature of such small intestinal findings may be surmised preoperatively

Figure 222, presented through the courtesy of Dr George Perakos of New Britain, Conn , reveals a small intestinal pattern almost identical with the preceding case But on operation this was proved due to regional enteritis

In most general hospitals one does not often have the opportunity to see intestinal tuberculosis, but in tuberculosis institutions such lesions are rather common A fairly typical example of tuberculous ileocolitis is shown in Fig 223 There is considerable deformity raggedness of marginal contour and mucosal distortion of the cecum and proximal ascending colon Similar but less prominent changes are seen in the terminal ileum Moderate irritability of the ileocecal area was observed fluoroscopically But radiologically the



Fig 221 Proven primary lymphosarcoma of ileum simulating regional enteritis Compare with Fig 222

appearance cannot be distinguished from non specific inflammation, amebiasis or any other specific infection or infestation Infrequently malignancy may simulate such inflammatory lesions Ulcerative intestinal tuberculosis is usually associated with obviously active pulmonary tuberculosis, and this may give the clue to the proper interpretation In the present case the chest radiogram demonstrated extensive pulmonary cavitation It is therefore our policy routinely to radiograph the chest of every patient suspected of having enteritis or entero-colitis

When the intestinal tract is affected by amebiasis the cecum is the site of predilection although other parts of the colon may be involved The terminal



Fig 222 Proven extensive regional enteritis simulating lymphosarcoma Compare with Fig 221

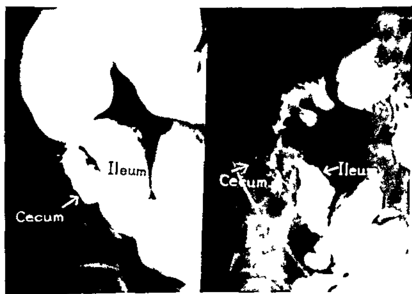


Fig 223 Ileocecal tuberculosis A chest radiograph disclosed extensive pulmonary cavitations



Fig 224 Amebic colitis showing progressive improvement under medical therapy A first examination B five weeks later C five months after A

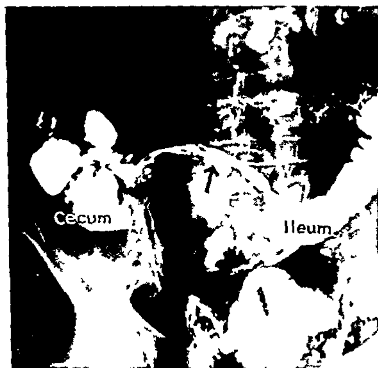


Fig 225 Extrinsic pressure on the terminal ileum by ovarian carcinoma masquerading as terminal ileitis

ileum is not frequently implicated When the cecum is affected, the roentgen appearance is not usually distinguishable from non-specific colitis or the specific infections or even malignancy Such a case is shown by Fig 224, a man with proven amebiasis At the time of our first examination, Fig 224, *A*, the cecum and ascending colon were narrow, stiffened, and exhibited moderate mucosal distortion, but the terminal ileum was fairly normal Because the organisms were found on stool examination, and the chest radiogram was negative, it was inferred that the *inflammatory changes in the right colon* were due to amebiasis The patient received anti-amebic therapy and on reexamination five weeks later slight but definite reexpansion of the cecocolic area was observed, Fig 224, *B* Our most recent examination, made five months after the first, shows considerable reexpansion of the proximal ascending colon and slightly more expansion of the cecum

An interesting circumstance is depicted in Fig 225 There is a long segment of narrowed terminal ileum presenting a fixed contour, and evidence of slight obstruction No small intestinal loops are adjacent to this segment In many respects the appearance suggests terminal ileitis But we reported it more likely due to extrinsic pressure by a pelvic tumor because the soft tissue outline of such a mass could be identified in a preliminary scout film, the contour of the terminal ileum corresponds with the upper margin of that mass, the marked displacement of the other small intestines suggests a mass much larger than the mesenteric thickening usually accompanying ileitis, *there is not as much distortion of the mucosal pattern as would be expected* if ileitis were present At operation an ovarian carcinoma was found, displacing but not invading the terminal ileum

It must be admitted, however, that the most common problem in differential diagnosis as we see it arises in the attempt to distinguish early stages of non specific enteritis and entero colitis from minor phases of small intestinal motor dysfunctions, or slight irritability in a colon not cleansed sufficiently to reveal its mucosal pattern Even when the first examination has been done carefully, in such doubtful cases an even more careful and detailed reexamination is usually required before one can decide whether or not organic pathology is present

SURGICAL TREATMENT

HERBERT R HAWTHORNE, M D

On our service at the Graduate Hospital in the last fourteen years, 31 patients with regional *enteritis or ileocolitis have been operated upon* We have had the opportunity to follow these patients, in conjunction with the Departments of Gastroenterology and Radiology The immediate results during the course of early follow up were very encouraging However, with longer and more adequate periods of observation, *it became evident that good results were not*

always permanent We were forced to reoperate upon many of these patients because of recurrence or progression of the disease Others manifested clinical or roentgenographic evidence of recurrences, but were maintained on intensive medical regimens These recurrences took place in spite of the fact that we employed a very radical operative approach and performed resection of the diseased bowel whenever possible From our observations of the gross and microscopic pathology, we believe that regional enteritis, ileocolitis and regional colitis are manifestations of the same disease in different segments of the intestine This does not include ordinary ulcerative colitis which of course first involves the sigmoid and rectum in 95 per cent of the patients and is, according to our present knowledge, a different entity clinically and pathologically

In our series we have seen five types of the condition classified as to location They are regional duodenitis jejuno ileitis, terminal ileitis, ileocolitis and regional colitis In 4 cases the lesion has been confined to the jejunum or ileum (not terminal) Eight cases had involvement of the terminal ileum Fifteen cases were examples of ileocolitis In two patients the site of involvement was limited to a segment of the colon, and in these there was no disease in the sigmoid rectum characteristic of distal ulcerative colitis In one case, the duodenum was involved in a process which grossly resembled chronic stenosing regional enteritis A lesion of this nature in this area has not been reported previously, as far as I know

PATHOLOGY

We have recognized three phases of this lesion the acute form, the chronic form and the chronic form with complications

ACUTE PHASE

The mimicry of acute appendicitis by regional enteritis is well known We have operated upon a patient for acute appendicitis and when the abdomen was opened the appendix was found to be normal but the ileocecal area was involved in the acute phase of regional enteritis In one, the serosa of the distal ileum was markedly hyperemic its texture was finely granular the subserosal tissues were edematous the glands in the adjacent mesentery were enlarged and hyperemic Appendectomy did not relieve this patient of her symptoms and roentgenographic survey a month later confirmed the presence of ileocolitis

The abdomen in the acute phase usually contains a small amount of free fluid The site of involvement may be any of the four previously described The fiery red and edematous loops of bowel stick together by thin friable, fibrinous adhesions The mesentery of the involved segment is moderately edematous and contains enlarged and congested glands In some instances the enlarged glands are confined to the mesentery of the diseased intestine in others, they may be widely scattered throughout the entire mesentery The submucosa is thickened and edematous The mucosa in this stage may be intact or shallow small ulcerations filled with mucopurulent debris may be

present In one patient (Fig 226), a preoperative diagnosis of subsiding acute appendicitis was made At laparotomy, we found an acute ileocolitis which appeared to be subsiding Resection, contrary to our usual practice was performed The specimen shows three large shallow ulcers These were filled with mucopurulent exudate and the mucosa between was hyperemic and markedly edematous

CHRONIC PHASE

When the chronic phase of this disease is reached, the gross picture changes The involved bowel is thickened and stiff The serosal surface may be covered with a fibroplastic exudate as seen in the acute phase, but often this has become organized into thick fibrous tissue which is contracted and stenoses the bowel The mucosa is hypertrophied and ulcerated and may be polypoid There is a marked thickening of all layers, but the submucosa shows the great



Fig 226 L S Acute ileocolitis with three large ulcers just proximal to the ileocecal junction

est increase The mesentery of the diseased bowel is usually thick, edematous and rubbery The overgrowth of antimesenteric fat is often marked (Fig 227) The lymph node enlargement varies from a slight increase in size to as large as 1 5 cm in diameter The node involvement is often widespread and well beyond the gross area of involvement This effect of the disease in the mesentery is a very apparent cause of failure in wide resections

CHRONIC PHASE WITH COMPLICATIONS

The chronic stage may be complicated by the presence of obstruction, peritonitis, abscess formation and fistulae Peritonitis of the spreading type from a free perforation has not occurred in our series The extreme thickening of the submucosa probably forms a strong barrier against rapid perforation of the ulcer Perforations usually occur late in the course of the disease and are walled off to form a localized abscess Burrowing into the mesentery is common This abscess, together with the involved bowel and mesentery,

forms a firm inflammatory mass The mass is extremely adherent with a broad base and is often situated along the course of the great vessels in the iliac fossa Therefore, the mass may not be resectable The abscess may perforate into adjacent bowel loops that are matted together and result in internal fistulas These fistulas may burrow externally through the abdominal wall

The appraisal of the extent of colonic involvement in ileocolitis has not been definite in many of our cases Some of the cases presented distinct evidence of advanced disease in the terminal ileum and cecum, but there was no abrupt termination of the process in the colon when external examination was made The colon that is extensively involved will show the same thicken



Fig 227 C B Demonstrates the marked overgrowth of antimesenteric fat that extends well down on the appendix

ing and contraction of the wall as is seen in the small intestine (Fig 228) In one of our cases there was a slight suggestion of edema and congestion of the wall of the colon with no gross involvement of the mesentery When the resected specimen was opened many mucosal ulcerations were found In our experience the mesentery of the colon is not as thick and edematous as is the mesenteric small intestine but is often firm and shortened due to fibrosis The presence of visibly affected glands varies and in several of our cases with advanced colonic disease, only minimal lymph gland involvement was noted

The complete classical picture of the gross pathology is not present in every case It should be stressed that many variations occur and are a source of confusion in the determination of the limits of the disease Perhaps this contributes to the high rate of recurrence following resection because the

lesion is not always completely eradicated For example, some cases do not show marked thickening and narrowing of the bowel but have a soft, flabby wall with no diminution in the size of the lumen Serosal exudate may be entirely lacking One may see great thickening of the mesentery with little or no overgrowth of fat on the serosal surface of the bowel Lymphadenopathy may range from minimal to widespread Furthermore, the picture in the

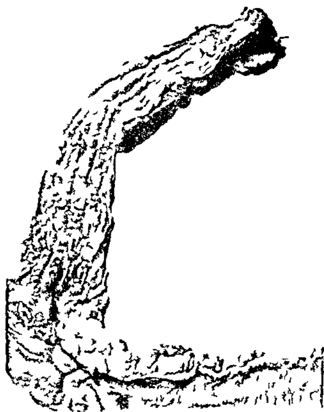


Fig 228 The thickened and contracted wall of the colon is well demonstrated with the typical gross appearance of the terminal ileum

chronic stage may be complicated by a superimposed acute exacerbation of the process

TREATMENT OF ACUTE PHASE

In considering the surgical treatment of this disease, it is necessary to define the stage of the pathologic process that is, the acute or the chronic phase with or without complications

A remission of the acute stage often can be obtained by rigorous medical management if an abscess or obstruction has not developed Even when these latter complications do develop, there is occasionally a subsidence of the acute phase while the patient is being prepared for operation A regression of the acute stage is not always followed by stenosis or other sequelae Some

do not progress to obstruction, abscess formation or fistulization It is in this category that we believe rigorous medical management, as outlined by Bockus, may have as much in its favor as surgical intervention No surgery should be attempted in a patient known to be in the acute stage of this condition without complication

In the cases that simulate acute appendicitis, exploration is advisable to rule out a pathologic process in the appendix If, after the abdomen has been opened, the appendix is found to be normal, and an uncomplicated acute ileocolitis exists, it is best to terminate the procedure Many feel that removal of the appendix under these circumstances is often followed by fistulas because the disease is actually present in the cecal wall and is not recognized Because of the likelihood of remission and the lack of preparation of the patient, we do not advocate resection of the lesion during this stage In fact, 3 of the 17 cases reported by Pugh were of this type and all subsided after laparotomy without definitive surgery If the picture is complicated by an abscess, drainage is necessary

SURGICAL TREATMENT OF CHRONIC PHASE

In the surgical management of the chronic stage, two types of operation are employed One consists of resection of the diseased bowel and primary anastomosis The other procedure is a transection of the ileum above the site of the lesion and anastomosis of the normal ileum to the colon distal to the lesion The ileal stump just above the lesion may be closed or brought out through a stab wound as a mucous fistula to act as a safety valve if the terminal ileum is partially obstructed

In our earlier experience with this disease, we assumed that wide excision of the involved ileum or colon would result in a cure A long segment of terminal ileum approximately 2 feet above the level of the disease and the proximal half or two thirds of the colon were usually resected In 2 patients all of the ileum and the right half of the colon were removed The mesentery was excised as close as possible to its base It was often impossible to remove every vestige of thickened mesentery and involved lymph glands without endangering the blood supply to the remaining bowel We felt that removal of the diseased bowel would allow the process in the remaining mesentery to subside

An early favorable response to this type of surgery caused us to continue with the method of attack however, later follow-up observations revealed that recurrences took place after the most radical resections

Resection of the diseased bowel was performed in 24 of the cases with 2 deaths in the earlier cases an operative mortality of 8 3 per cent Five of the resections have been followed for less than a year and should be excluded from the series when results are considered This is important because all but one of our recurrences took place after one year had elapsed One patient died of malnutrition one month after surgery and another patient was lost for follow up purposes There remain 15 patients who have been carefully followed from one to fourteen years Eleven recurrences based on clinical

lesion is not always completely eradicated For example, some cases do not show marked thickening and narrowing of the bowel but have a soft, flabby wall with no diminution in the size of the lumen Serosal exudate may be entirely lacking One may see great thickening of the mesentery with little or no overgrowth of fat on the serosal surface of the bowel Lymphadenopathy may range from minimal to widespread Furthermore, the picture in the

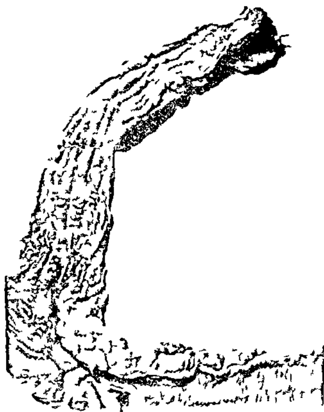


Fig 228 The thickened and contracted wall of the colon is well demonstrated with the typical gross appearance of the terminal ileum

chronic stage may be complicated by a superimposed acute exacerbation of the process

TREATMENT OF ACUTE PHASE

In considering the surgical treatment of this disease, it is necessary to define the stage of the pathologic process that is, the acute or the chronic phase with or without complications

A remission of the acute stage often can be obtained by rigorous medical management if an abscess or obstruction has not developed Even when these latter complications do develop, there is occasionally a subsidence of the acute phase while the patient is being prepared for operation A regression of the acute stage is not always followed by stenosis or other sequelae Some



Fig 229 Large inflammatory mass with internal fistulas between the sigmoid and lower ileum.



Fig 230 Disappearance of fistulas and mass three years after ileostomy

and roentgenographic examinations have taken place in those 15 cases—a recurrence rate of 73 per cent (Tables 33 and 34)

These discouraging results have caused me to modify my views, and in the past two years, I have elected to use ileocolostomy with exclusion of the diseased bowel in 6 cases The results of Garlock and others with this type of operation have been exceptionally good, and the surgical mortality is very low

The cases of chronic stenosing regional enteritis which are classified as complicated are best treated by the short-circuiting and exclusion operation The case with a large abscess walled off by adjacent loops of diseased bowel and complicated by an infiltrative process in the mesentery cannot be resected safely Large obstructing inflammatory masses can also be treated by a side tracking operation with less hazard Similarly, when the diseased bowel is densely adherent to the posterior parietes or to the vessels along the lateral

Table 33 Results of Radical Resection

Total Number of Resections		24
Operative deaths	2	
Cases followed less than 1 year	7	
	9	
Cases closely followed from 1 to 14 years		15
Number of proved recurrences		11
Recurrence rate		73%

(Hawthorne and Frobese Ann Surg August 1949)

Table 34 Time Elapse Between Resection and Recurrence

	No of Cases
1–2 years	5
2–3 years	3
3–5 years	1
5–10 years	2
Total	11

(Hawthorne and Frobese Ann Surg August 1949)

pelvic wall, it is unwise to attempt a resection Internal and external fistulas are further indications for ileocolostomy with exclusion

The 6 cases in which we performed this type of operation were all complicated ones Two had had radical resections before, but had developed recurrences In addition, a gastrojejunostomy was performed on the patient with duodenal involvement Four of these remain symptom-free after a two year follow-up In one case, a transection of the terminal ileum and ileo transverse colostomy with exclusion was performed One year later, there was a definite recurrence in the ileum proximal to the anastomosis The patient was re-operated and the ileum was transected above the site of the recurrence and anastomosed to the distal transverse colon The distal stump of transected ileum was brought out as a mucous fistula The inflammatory mass present in the right iliac fossa at the first operation had entirely disappeared All gross

cised and the remaining ileum was anastomosed to the ascending colon When this resected segment of ileum was opened, small mucosal ulcerations were noted and microscopy revealed the typical tubercle like nodules in the lymphoid tissue of the submucosa We believe that this man will have a recurrence at the anastomotic site

SUMMARY

In our early experience with this disease we performed radical resection of the diseased bowel with the hope that a cure would result In the ensuing years, recurrences took place in such a large percentage of the cases that I am convinced that resection is no longer the procedure of choice

The less radical procedure of exclusion advocated by Garlock has accomplished as much, and even though we have had recurrences from this type of operation it is attended with much less morbidity and mortality

It is difficult to understand our large percentage of failures following resection when the results are compared with those from other clinics practicing resection Our cases have all been carefully followed by the Departments of Surgery, Gastroenterology and Radiology Under such close scrutiny, some who were clinically well were eventually found to present some evidence of recurrence We can only assume that longer and more intensive follow up surveys in series from other clinics will reveal a higher recurrence rate

As a result of our experience with this condition, we believe that surgical intervention should be confined to those cases complicated by obstruction, abscess or fistulas, and those in which a most thorough medical regimen has failed

evidence of disease in the excluded ileum had disappeared This section of bowel was found to be soft and collapsed and the serosa was pale and shiny No enlarged glands were present in the mesentery The entire colon appeared normal Six months after the second operation, the disease again became active, and roentgenographic study revealed a second recurrence at the anastomotic site Exploration was undertaken again and the colon distal to the anastomosis was markedly involved This is of interest because the process had previously been confined to the small bowel, but recurrence took place in the colon An ileostomy was necessary to divert the fecal stream from the diseased bowel The patient died three months later of inanition

The presence of widespread mesenteric lymph gland involvement is an indication for the exclusion operation Cases with extensive involvement of the small intestine or multiple "skip areas" should be treated conservatively One of our patients was operated on elsewhere by a surgeon well trained in the recognition of this process Four skip areas were present in the ileum, therefore, he closed the abdomen without any surgical attack on the lesions She was treated medically for three years and finally died following our attempt to relieve a multiple obstruction We believe that his keen judgment allowed this patient three years of uncomplicated survival

Occasionally a patient with involvement of the terminal ileum and the colon from the cecum to the sigmoid is seen In this instance, we elect to do an ileostomy well above the site of the disease in the ileum If the lesion becomes quiescent and does not progress into the distal sigmoid, restoration of bowel continuity by ileosigmoidostomy may be attempted It is wise to observe these patients for a period of two to three years before restoration of continuity We have not encountered a lesion where such a procedure was deemed advisable One case had an extensive enteritis in the terminal ileum complicated by an obstructing mass adherent to the sigmoid colon The sigmoid was involved by contiguity and internal fistulas were present (Fig 229) An ileostomy was made well above the lesion The patient improved markedly (Fig 230), and three years later, he insisted that the ileostomy be taken down At the second operation, the distal sigmoid was found to be slightly involved in some congested dense adhesions Therefore, the terminal ileum was anastomosed to the ascending colon, and a colostomy proximal to the area of the previous sigmoidal obstruction was performed We assumed that a left sided colostomy would be easier for the patient to care for than a high ileostomy The colon from the cecum to the sigmoid had remained free of involvement, but further observation of the distal sigmoid was definitely indicated before restoration of complete continuity At the second laparotomy, it was noted that the excluded ileal segment which had been badly diseased appeared normal The mass along the sigmoid and the fistulous tracts had all disappeared The only evidence of old inflammation was the area of moderately congested adhesions on the distal sigmoid colon The ileum proximal to the *ileostomy appeared normal*, however, after the slight trauma of inspection and palpation, the serosal surface became edematous and hemorrhagic Therefore, a segment 35 cm in length above the ileostomy was ex-

Intestinal Obstruction

Intestinal Obstruction

CLASSIFICATION OF TYPES AND CLINICAL FEATURES

HENRY J TUMEN, M D

The purpose of this introductory talk is to give a brief outline of the general problems involved in the discussion of intestinal obstruction and to present an outline of the general clinical features and the general problems in diagnosis, and that probably is best begun by discussing some of the problems concerned with classification of types

THE CLASSIFICATION OF INTESTINAL OBSTRUCTION

Any case of intestinal obstruction may be classified in a number of different ways

These include

I Location of the Obstruction
- High small intestinal
- Low small intestinal
- Colonic

II Integrity of the Intestinal Blood Supply
- Simple obstruction
- Strangulation obstruction

III The Development of a Closed Loop

IV The Acuteness of the Obstruction

V The Presence of a Mechanical Obstruction in Contrast to a Disturbance of Peristaltic Activity

VI The Specific Etiology

One of the most important features in regard to the classification of intestinal obstruction is the question of *location of the obstruction* whether it involves the upper part of the small intestine the lower part of the small intestine or the colon The importance of this distinction is quite obvious if you consider what happens during the various types of obstruction that involve these different areas of the bowel In high intestinal obstruction as will undoubtedly be brought out by the subsequent speakers, the characteristic features are marked vomiting entailing the loss of large amounts of fluid the tremendous changes in the electrolytic balance and the general tendency for the marked distention not to occur In other words the principal feature of high small intestinal obstruction is fluid loss and electrolyte loss In low small intestinal obstruction vomiting is a later symptom While fluid and electrolyte loss occurs, it is not as prominent a manifestation There is the important factor of distention of the small bowel, which produces

a number of problems in itself That results, of course, in loss of fluid into the bowel, *changes in the bowel wall* and *possible absorption* of so-called toxic materials from the bowel Colonic obstruction is again a different entity, very often because clinically it has a more insidious onset Vomiting is even less likely to occur and may be entirely absent, distention of the colon is very often quite pronounced and that occurs particularly if there is competency of the ileocecal valve

Another point in the classification of intestinal obstruction is the question of *preservation of the blood supply* whether or not the obstruction in question is one of so-called simple obstruction or whether there is strangulation obstruction This term is used to indicate that there has been a disruption of the circulation of the bowel, arterial or venous or both, a change which in itself produces dire consequences so far as the patient is concerned, resulting in much greater damage to the bowel wall and the possibility of rupture of the bowel and changes within the peritoneum The question of the recognition of strangulation is probably the most important single factor from the clinician's standpoint in the approach to the management of the patient with intestinal obstruction, because of the necessity for discarding a conservative program of therapy and the need for institution of a radical surgical approach Ordinarily the clinical manifestations of strangulation obstruction are the relatively acute and dramatic onset, the evidence of shock early in the course of the obstruction, the presence of pain that is more constant, more severe with less tendency to the general colicky pain that is characteristic of most simple obstructions, the characteristic presence of abdominal tenderness, fever and leukocytosis, signs which are very often absent in ordinary simple and uncomplicated obstruction

One of the most important things to say about the recognition of strangulation obstruction is the fact that its absence early in the course of obstruction does not preclude the possibility that it may develop at any time during the course of obstruction A patient who is seen today and who apparently doesn t have strangulation may develop that complication a few hours later or the next day, or any time during the existence of obstruction This makes it extremely incumbent upon the physician in charge of the patient with intestinal obstruction to keep the patient under constant observation so that if strangulation should develop during the course of conservative management a change in approach can be planned

Another means of classifying intestinal obstruction is the question of development of what is called a *closed loop* That term is applied to the type of obstruction in which both ends of the obstructed area of the bowel are blocked off fairly completely so that nothing can move in either direction This results, of course, in tremendous distention of the loop involved and changes in the bowel wall which are more pronounced than in other types of obstruction The term is used very often to apply to the types of obstruction that are associated with volvulus of a portion of the bowel or blocking off of a portion of the bowel as a result of being caught under a loop of adhesions It also is applied very often to colonic obstruction again because in

colonic obstruction with competence of the ileocecal valve there is ability for material to move into the colon from the small intestine, but not get back into the small intestine The result is that the colon undergoes a progressive distention which may become extremely marked and result eventually in rupture of the bowel

Another point in classification is the question of the *acuteness of the obstruction* an obstruction that comes on very suddenly, very acutely, will result in a much more dramatic course and one that is much more damaging to the general economy of the patient than a slowly developing obstruction to which the patient can adjust for some period of time and, in a certain sense, compensate for

Distinction should be made between *mechanical obstruction and a disturbance in peristaltic activity* This is a classification that is extremely important because, as a matter of fact, the various types of mechanical obstruction have very little in common with the obstruction or ileus that results from defects in the peristaltic function of the bowel musculature The various complications of obstruction strangulation perforation of bowel etc, are much less likely to occur, if they occur at all, in the patients who simply have disturbed peristaltic activity, also now that we know a great deal more about the treatment of intestinal obstruction by intubation, the patients who have ileus solely on the basis of disturbed bowel function are treated best and most efficiently by intubation as contrasted to operation

And then finally of course there is an attempt to classify obstruction on the basis of its *specific etiology*

THE CAUSES OF INTESTINAL OBSTRUCTION

- I Mechanical Obstruction
  - A Narrowing of the Lumen
    - 1 Strictures
      - a Congenital Atresias
        - Imperforations
        - Inflammatory
      - b Acquired Traumatic
        - Vascular
        - Neoplastic
    - 2 Obturation Gallstones
      - Fecoliths
      - Foreign bodies
      - Worms
    - 3 Compression from Without
  - B Obstruction from Adhesions or Bands Congenital
    - Inflammatory
    - Traumatic
    - Neoplastic
  - C Hernia External
    - Internal
  - D Volvulus
  - E Intussusception

II Obstruction Due to Nervous Imbalance
 A Inhibition ileus
 B Spastic ileus
III Vascular Obstruction
 A Thrombosis
 B Embolism

This outline, which is a modification of the classification that has been introduced by Wangensteen and widely used, is, of course, simply a listing of a great many causes of obstruction It brings out the tremendous variety of different etiologic backgrounds for which we have to look in the management of a patient with intestinal obstruction It is important to note, of course, that most of these are extremely rare and that when we are interested in a specific case of intestinal obstruction, it is most important to know the relative incidence of these various causes

If we limit our discussion for the next few minutes to mechanical obstruction, and consider particularly the adult, we know that approximately 10 per cent of cases of intestinal obstruction are the result of neoplasms of various types, approximately 40 to 50 per cent result from hernias and about 20 to 30 per cent result from the various adhesions In other words, if we consider solely the obstruction that occurs in the adult, from 65 to 80 per cent of all intestinal obstruction is the result of a hernia that has become strangulated or incarcerated, or of postoperative adhesions, and for that reason we can make two generalizations We can say first of all that in a patient who has had a previous abdominal operation and who is now suffering with abdominal pain, one of the most important things to consider as the cause for that pain is *intestinal obstruction, and we can also say that in any patient* who has intestinal obstruction, one of the most important points in examination is to determine whether or not a hernia is present or whether or not there is a scar on the abdomen which may indicate that there are intra abdominal adhesions

SYMPTOMS OF MECHANICAL OBSTRUCTION

In general, mechanical obstruction has certain characteristic symptoms that we all recognize These are abdominal pain, vomiting and obstipation Of these, pain is certainly the most typical Characteristically the pain of mechanical obstruction is an intermittent pain, what is truly to be defined as a colicky type of pain that goes through paroxysms of increased and decreased intensity with intermittent periods of relative freedom from pain during which the patient feels relatively well One of the most important features, from a clinical standpoint, of this type of pain, is its association with hyperperistalsis, hyperperistalsis that the patient recognizes himself and will describe as occurring synchronously with the pain, hyperperistalsis that we can recognize by physical examination From the standpoint of the examination of the patient who has possible intestinal obstruction, probably the most important single thing to do is to listen to the abdomen carefully during the time that the patient has pain in order to determine whether or not hyperperistaltic activity is going on synchronously with the pain that the patient has

As the obstruction continues, there is a gradual tendency for the pain to become more constant, to lose its intermittent nature and gradually to merge into a fairly constant discomfort with periodic exacerbations As I said before, that is particularly true when strangulation develops, because under those circumstances there is also a tendency for loss of the colicky nature of the pain and a gradual development of pain that is fairly constant

Another feature of the progressive pain that these patients suffer is the tendency for the abdomen to become distended as the clinical course proceeds Vomiting is another feature of intestinal obstruction to which a great deal of importance attaches, not only to the symptom but because of its influence on the general physiology of the patient Vomiting, as I ve already said, is most characteristic of high, small intestinal obstruction, it occurs, of course, with low small intestinal obstruction and gradually, as the intestine empties by reverse peristalsis or by the gradual reflux of fluid into the stom ach there is tendency for the so called fecal or feculent vomiting to occur I think it is important to stress that vomiting does not always occur in intestinal obstruction It may not occur until relatively late in individuals who have obstruction low in the small bowel and it may never occur in colonic obstruction To exclude a diagnosis of intestinal obstruction because the patient has not vomited is very often a dangerous thing to do That has been particularly stressed in the cases of colonic obstruction associated with a competent ileocecal valve In those patients progressive distention of the abdomen and the progressive recurrence of pain without vomiting are char acteristic features that point to low colonic obstruction with competent ileocecal valve

The obstipation of obstruction, of mechanical obstruction is another feature which is stressed in statistical discussion of obstruction, but which again may not be as complete or absolute in a given patient as we very often are led to believe Intussusception is one type of obstruction in which con stipation doesn t occur and in which in fact the patient may have diarrhea In some colonic obstructions, constipation doesn t occur immediately with the onset of obstruction There is a tendency for the colon to try to empty itself below the obstruction The initial bout of pain may not be associated with constipation because the patient takes an enema and empties his lower bowel and in the strict sense of the word can t tell you that he s been con stipated What is true of most patients with obstruction is that once the obstruction has come on and become complete, there is the tendency for the bowels not to move and particularly for the patient not to pass gas spon taneously

Now in many instances of course it is true that the signs the clinical evidence of obstruction may be relatively slight Patients do not always give the characteristic history their pain may be relatively slight, they may not vomit immediately, they may not be constipated immediately If the patient is permitted to go on for a while obstructed, he does become distended, he does if you listen carefully have hyperperistalsis but it is very important to be suspicious of obstruction early if proper treatment is to be given and

if the mortality is to be kept low For that reason we feel that it is important to stress a suspicious attitude in regard to obstruction and to use the single laboratory procedure that is most valuable in the differential diagnosis of obstruction, frequently and early, and very often unnecessarily therefore, in order to be sure that obstruction does not exist I'm referring, of course, to the fact that of the various objective methods for diagnosing obstruction, the most important, the most characteristic, is the use of the scout film of the abdomen to determine whether or not there is a distended bowel loop

There is no necessity for going into the various x-ray characteristics of intestinal obstruction, I think it is sufficient to say that this is the most essential and critical of the various objective methods by which obstruction can be recognized Fortunately, the x ray evidence begins very promptly after obstruction Within the course of a few hours after an obstruction has come on, the patient shows characteristic x ray features which can usually be recognized by any one who is at all familiar with this particular problem The simplest thing to do whenever the question of obstruction has been raised in a given case is to subject the patient to an x ray examination by scout film and, if there is any reservation at all, simply keep the patient waiting another hour or two with the knowledge that that period of time should ordinarily suffice for definite signs of obstruction to come on and a definite diagnosis to be established

A presentation of any list of the causes of obstruction and a brief discussion such as this are important for one very important reason, and that is to emphasize that intestinal obstruction is not a disease in itself It is a symptom rather than a disease entity In discussing its clinical importance, I wish to emphasize the various important features of the symptom, the level of the bowel involved, the presence of strangulation, the presence of the closed loop which leads to excessive distention of the bowel, the differentiation, if possible, of mechanical obstruction, and an attempt to recognize the underlying cause so that the proper therapy and the planning for its removal can be instituted

BIOCHEMICAL ASPECTS OF INTESTINAL OBSTRUCTION

DAVID L DRABKIN, M D

Knowledge of the biochemical alterations which are associated with obstructive disease of the intestine has been of great value in the understanding of the fundamental derangement under such circumstances, as well as in directing effective therapy Dr Bockus has asked me to discuss, particularly, the subjects of hypochloremia, alkalosis and hyperazotemia, thereby limiting the

range to the conjoined problems of the body s water and acid base balance Acute pyloric obstruction happens to be the major clinical condition in which we find alkalosis of the type which has been described as *'primary alkali excess,* although, as will be seen, actually the primary factor is that of acid loss from the body Acute pyloric obstruction is also among the main clinical conditions in which *dehydration,* a more serious consequence than that of displacement from the norm of acid base balance, is prone to occur and rather rapidly

WATER BALANCE AND INTERMEDIATE WATER EXCHANGE

It may be well at the risk of appearing academic, to speak at the outset of some simple things by way of orientation and without the encumbrance of detail The largest component of the body, about 70 per cent of the total mass, is water In a 70 kg man this would amount to 49 liters or 49,000 ml of total body water, of which approximately 35,000 ml are *intracellular* and 14 000 ml are *extracellular* The extracellular compartment is in turn, regarded as composed of a *vascular* space i e, the blood plasma, whose dimension is of the order of 3000 ml, and the *interstitial* fluid, which forms the remainder of about 11 000 ml There is, of course, no rigid subdivision in these fluid compartments They are in equilibrium with each other However it is important to stress that equilibrium need not denote equality or identity (see osmotic balance, below)

The over all water balance of a 70 kg body, in fluid equilibrium with its external environment, may be given by such values as Intake = 2000 to 2500 ml, Output = 2000 to 2500 ml Such balance studies do not disclose metabolic transactions (in water) of far larger magnitude, which may be designated the *intermediate water exchange* Thus, the volume of total gastro intestinal secretions produced *per day* is about 10,000 ml, while the daily formation of gastric fluid in which we are presently interested is about 1500 to 2500 ml Also, per day some 180 liters of fluid are filtered through the glomeruli—yet only 1000 to 1500 ml of fluid are lost from the body as urine Since blood plasma volume is normally quite rigorously maintained (one expression of homeostatic control) it becomes obvious that the over all fluid balance of relatively small magnitude (2 to 2 5 liters) is only possible by the continuous operation within the body of a vast fluid conservation activity Prime organs in this intermediate fluid exchange are the kidneys and intestines The valid inference is that we reabsorb practically all of the water *as well as its dissolved constituents* from our gastrointestinal secretions Failure to do so, for one reason or another, creates trouble—an excellent example of which is to day s problem, the undue loss of fluid through severe vomiting in intestinal obstruction This is the crux of the matter

OSMOTIC BALANCE

The above is somewhat too simple, so let s make it just a little more complicated Body water is not water alone It is a complicated solution containing salts besides other things such as glucose urea and some protein

Furthermore, a salt, such as sodium chloride, NaCl, does not maintain its identity when dissolved in water, but promptly splits up or dissociates into two discrete particles, one positively charged, the sodium cation, Na^+, the other negatively charged, the chloride anion, Cl^- Since the positive and negative charges balance, the solution is electrically neutral and remains so, but each particle or ion now exerts its own separate influence on the water in which it is contained Water itself has an interesting property It does not like to stay within containers It has a *characteristic escaping tendency* It is this escaping tendency which is at the basis of the familiar assumption that water is freely diffusible across cellular membranes The presence of such ions in water as Na^+ and Cl^- serves to restrain the escaping tendency of water, serves to keep water "in We are actually discussing *osmotic pressure*, which is really a measure of the extent to which dissolved particles interfere with the escape of water Ions, therefore, are osmotic factors Water within the body is a solution of osmotic factors As water is lost from the body, osmotic factors are lost at the same time The sum of water balance and acid-base or ionic balance is *osmotic balance* Uncompensated loss of body fluids (water plus osmotic factors) leads to *osmotic imbalance* Ions or other osmotic factors and water are biologically inseparable, go hand in hand Dehydration is an expression of an osmotic imbalance state

Several additional points may be made

(1) It is remarkable that all the body fluids, intra- and extracellular, and the individual gastrointestinal secretions are practically iso osmotic with each other (have practically the same content of osmotic factors) The shed urine, which in reality is no longer a body fluid, is exceptional Its molar concentration of osmotic factors may be as much as four times that of the various body fluids

(2) It is equally remarkable that, despite their similar total osmotic character, the individual patterns of the ionic composition of the body fluids may be very different Thus, potassium, K^+, is the predominant cation of intracellular water, whereas Na^+ is predominantly, nearly exclusively, though not quite, extracellular The gastric secretion is practically iso-osmotic with blood plasma (as will be evident shortly), and also with the pancreatic and intestinal secretions But gastric fluid, owing to its high concentration of hydrogen ion, H^+, is very acid in reaction whereas the intestinal secretions are slightly more alkaline than the blood plasma In this connection, it is appropriate to refer to the location of the obstruction, a point which Dr Tumen wisely made in his classification of intestinal obstruction states For example, if the obstruction is at the pylorus, the vomitus is solely gastric fluid On the other hand, if the obstruction is lower down, a combination of acid gastric fluid and alkaline intestinal fluid may be lost from the body *In either case, water and osmotic factors will be lost, and dehydration may ensue* In acute pyloric obstruction, owing to the peculiar ionic pattern of the fluid lost, dehydration will be accompanied by alkalosis In obstructions lower down, the mixture of fluids lost may be such, by chance, that only slight change in the pH of the blood may be found

(3) Another point in Dr Tumen s classification, the *speed of onset or development of the condition* has biochemical pertinence Mothers, and, doubtless, infant sufferers from *chronic vomiting* do not like this condition However, pediatricians recognize that, while a slight alkalosis may be present in infants with chronic vomiting frank dehydration rarely develops The kidneys remain functional and the condition is well tolerated Acute pyloric obstruction is very different indeed With severe uncontrolled vomiting dehydration may develop rapidly, and, attending this state, one may expect at least some, and, *frequently severe kidney disability* This is a very important complicating factor The kidneys are the final arbiters of the body s acid-base and water balance We shall return to this point Therapeusis in dehydration states must be directed not only with the view of correcting the deficits of ions and water, but also towards restoring kidney function The latter is a paramount consideration particularly in the use of replacement solutions, designed to correct for cellular loss of K^+ The speed with which unusually severe alkalosis and dehydration may develop is dramatically illustrated in certain cases in which Wangensteen gastric drainage is instituted Suction drainage may stimulate the stomach to produce more fluid In place of the usual 2 liters 6 liters may be produced per day Under these circumstances it may take only six to twenty four hours to develop severe acid base and osmotic imbalance

One should not assume that the untoward loss of gastric juice need always result in alkalosis If the underlying condition, in which pyloric obstruction has developed is one in which hydrochloric acid is low or absent, naturally this will have an influence on the picture which is reflected in the chemistry of the plasma Also the previous nutritional state of the individual must be considered Thus, in the severe vomiting which may accompany the toxemias of pregnancy, reports in the literature appear to be confusing—some indicate alkalosis others acidosis Both are possible Alkalosis may be expected in a previously well nourished individual, who suddenly starts to vomit large quantities of the acid gastric fluid On the other hand if relative starvation has been present starvation ketosis (acidosis) enters the picture and one need not expect the frank alkalosis evident in the first type of case

(4) Finally, before showing my single slide, I would like to say a word about a subject sometimes found unpleasant When one deals with osmotic considerations as we do at present, one is forced to use a notation appropriate to this subject Fundamentally, osmotic influence the restraining influence upon the escaping tendency of water is a function not of the weight of the dissolved materials but of the number of particles or molecules per unit volume Hence we can discuss acid base and osmotic phenomena intelligently only in molecular or molar concentration terms For that matter, all of the body s chemical reactions have to do with reacting molecules Hence though difficulties there may be the proper language must be learned and used I am sure that most of you have already mastered this language and thus have already learned how superior it is, and actually how much easier it is to remember and use than the old language of the exchange

Furthermore, a salt, such as sodium chloride, NaCl, does not maintain its identity when dissolved in water, but promptly splits up or dissociates into two discrete particles, one positively charged, the sodium cation, Na^+, the other negatively charged, the chloride anion, Cl^- Since the positive and negative charges balance, the solution is electrically neutral and remains so, but each particle or ion now exerts its own separate influence on the water in which it is contained Water itself has an interesting property It does not like to stay within containers It has a *characteristic escaping tendency* It is this escaping tendency which is at the basis of the familiar assumption that water is freely diffusible across cellular membranes The presence of such ions in water as Na^+ and Cl^- serves to restrain the escaping tendency of water, serves to keep water 'in We are actually discussing *osmotic pressure*, which is really a measure of the extent to which dissolved particles interfere with the escape of water Ions, therefore, are osmotic factors Water within the body is a solution of osmotic factors As water is lost from the body, osmotic factors are lost at the same time The sum of water balance and acid-base or ionic balance is *osmotic balance* Uncompensated loss of body fluids (water plus osmotic factors) leads to *osmotic imbalance* Ions or other osmotic factors and water are biologically inseparable, go hand in hand Dehydration is an expression of an osmotic imbalance state

Several additional points may be made

(1) It is remarkable that all the body fluids intra- and extracellular, and the individual gastrointestinal secretions, are practically iso osmotic with each other (have practically the same content of osmotic factors) The shed urine, which in reality is no longer a body fluid, is exceptional Its molar concentration of osmotic factors may be as much as four times that of the various body fluids

(2) It is equally remarkable that, despite their similar total osmotic character, the individual patterns of the ionic compo ition of the body fluids may be very different Thus, potassium, K^+, is the predominant cation of intracellular water, whereas Na^+ is predominantly, nearly exclusively, though not quite, extracellular The gastric secretion is practically iso-osmotic with blood plasma (as will be evident shortly), and also with the pancreatic and intestinal secretions But gastric fluid, owing to its high concentration of hydrogen ion, H^+, is very acid in reaction, whereas the intestinal secretions are slightly more alkaline than the blood plasma In this connection, it is appropriate to refer to the location of the obstruction, a point which Dr Tumen wisely made in his classification of intestinal obstruction states For example, if the obstruction is at the pylorus the vomitus is solely gastric fluid On the other hand, if the obstruction is lower down, a combination of acid gastric fluid and alkaline intestinal fluid may be lost from the body *In either case, water and osmotic factors will be lost, and dehydration may ensue* In acute pyloric obstruction, owing to the peculiar ionic pattern of the fluid lost, dehydration will be accompanied by alkalosis In obstructions lower down, the mixture of fluids lost may be such, by chance, that only slight change in the pH of the blood may be found

osmotic purposes) but in mEq/LH_2O This is so, since most of the ions in body fluids are univalent If we compare the total of ionic concentrations in the gastric juice with those in the normal blood plasma (first diagram of the lower group), we find that in each case the positive and negative ions summate to about 160 mEq/LH_2O This, again is in line with the fact that body fluids as different as gastric juice and blood plasma, are, nonetheless, similar os-

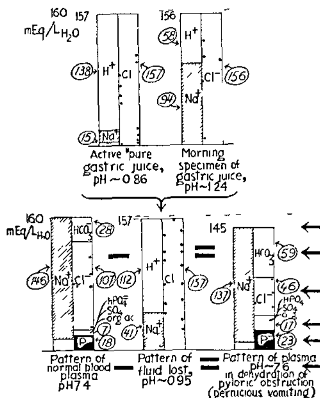


Fig 231 Ionic diagrams (composition in mEq /LH_2O) of gastric fluid and of the blood plasma before and after unrelieved loss of the former

The upper diagrams show composition of pure gastric fluid uncontaminated by protein etc It is assumed that the pattern of fluid lost is intermediate between that of active and resting fundic gastric secretion

The lower diagrams illustrate the reflection of untoward loss of the acid gastric fluid in the composition of the altered or pathologic plasma

This figure is taken from a manuscript for a text by the writer in preparation for publication by the Williams and Wilkins Company

motically At this stage it may be seen that in both cases the total of positive charges (total of cations) exactly equals the total of negative charges (total anions) This is required since, regardless of pH (very acid gastric fluid of pH 0 86—1 24 and slightly alkaline plasma fluid of pH 7 4) electrical neutrality (equality of total opposite charges) must be maintained There can be no homeless or unbalanced positive or negative ions

counter The biological magnitudes are such that one can use appropriate whole numbers, when ionic concentrations are expressed not as mols (gram molecular weight) per liter, but as millimols (milligram molecular weight) per liter, mM/L A related term, frequently employed, is milliequivalents per liter, mEq/L mEq/L has the same relationship to mM/L that a normal solution has to a molar In the case of univalent (singly charged ions), such as Na^+ or Cl^-, normal and molar quantities are the same In the case of di or bivalent ions, as Ca^{++} or $SO_4^{=}$, a molar solution is equal to a 2 normal solution We shall express concentrations in the ionic diagrams in terms of mEq/L_{H_2O}, i e per liter of water, not per liter of solution Plasma, for example, contains approximately 93 per cent of water Therefore, if the concentration of Cl^- is 100 mEq per liter of plasma, it will be 100/0 93, or 107 mEq/L_{H_2O}

ACUTE PYLORIC OBSTRUCTION

With these introductory remarks, we may now present Fig 231, which illustrates, by means of ionic diagrams, how the altered composition of the blood plasma reflects the untoward loss from the body of a highly acid fluid, the gastric secretion, in a typical, severe case of acute pyloric obstruction, in which compensating factors (lung and kidney function) have broken down or are inadequate to meet the need, and in which uncompensated, marked alkalosis and dehydration are at hand

Let us take up systematically several points, illustrated in this figure

(1) *Variability of the Gastric Secretion* The upper set of ionic diagrams illustrates the large variations which are normally found in the ionic pattern of gastric fluid They are an expression of the well-known fact that "active gastric juice is more highly acid (contains more free hydrochloric acid) than gastric juice produced by the resting stomach You may note that both specimens contain the same concentration of chloride, Cl^-, the negative ion or anion This is consonant with the fact that total chloride is relatively constant in both "active" and "resting gastric juice, the difference in composition being related to the relative concentrations of HCl and NaCl in the two samples, which may be inferred from the concentrations of individual ions, H^+ and Na^+, circled in the diagrams In the case of all body fluids, Cl^- is the preponderant anion In the case of "pure gastric juice it is practically the exclusive anion It is also of interest that, whereas the amount of hydrogen ion, H^+, is about twice as great in the active juice as in the other, the pH is only a little lower, pH ~0 86 and ~1 24 Both specimens are highly acid This is owing to the fact that HCl is a strong acid, and not much of it is necessary to lower the pH markedly in a relatively poorly buffered fluid, such as pure gastric juice (practically free of or very low in protein) It may also be pointed out that the two upper diagrams suggest that both samples of gastric secretion, though different in ionic pattern, have similar total *osmotic characteristics* Reference has already been made to this point This inference may be validly drawn from such diagrams, despite the fact that the notation is not in mM/L_{H_2O} (the only strictly proper one for

reduced K^+ in blood plasma, *hypopotassemia* or *hypokaliemia* Hypopotassemia may accompany potassium cytopenia, but, more often in untreated frank dehydration, there may actually be an elevation in the concentration of serum K^+, despite the impoverishment of this ion in intracellular fluid (see later)

Certain features on the anionic side are of particular interest First, the bicarbonate anion, HCO_3^-, forms about one fifth, in comparison with Cl^- which is three fifths of the total anions of blood plasma The HCO_3^- is a measure of the *alkaline reserve* (Van Slyke and Cullen), which is that fraction *of the total cations or fixed base of the type of* Na^+, *which is associated* with or subtends or balances the HCO_3^- Bicarbonate is the most labile anion of blood plasma and of extracellular fluids It is the anion of the weak est acid (carbon dioxide or carbonic acid) present in measurable amounts in blood plasma, and, hence bicarbonate readily reacts with any stronger acids which may momentarily, in metabolism, invade the blood Thus, the meas urement of HCO_3^- concentration affords an index of departure from normal acid base balance *The bicarbonate goes down in acidosis up in alkalosis* Not shown in the diagram is the concentration of free CO which represents the amount of carbonic acid H_2CO_3 in blood plasma The amount under normal conditions is one twentieth of that of the bicarbonate anion You are doubtless more familiar with the expression volumes per cent of CO_2' the *carbon dioxide content* as a measure of the *alkaline reserve* of the plasma This is an illustration of some of the inconsistencies of notation to which we have become inured but which, for clear thinking, it is desirable to avoid The CO content is determined by the familiar gasometric procedure in which by means of added acid all of the bicarbonate is converted to CO_2 For example, per liter of blood plasma there are actually present 26 mEq/L of HCO_3^- and only 1 3 mEq/L of free CO_2 In the analysis, the bicarbonate is converted into CO and therefore we express in volumes of gas some thing 95 per cent of which in blood is not a gas at all, but an inorganic anion To convert 26 mEq/L of HCO_3^- into volumes per cent (ml per 100 ml) of CO_2, the gas factor 2 24 (derived from 22,400 ml, the volume occupied by 1 mol of a gas under standard conditions of pressure and temperature) is used 26 mEq/L $\times$ 2 24 = 58 3 vol / CO which represents bicarbonate In the same way, 1 3 mEq/L $\times$ 2 24 = 2 9 vol % (the actual free CO_2) Now, 58 3 + 2 9 = 61 2 vol % the familiar normal value for the total CO_2' content

I am going to chance once again the probability of being stamped with the label of pedagog by a further preachment of the gospel of milliequiva lents A group of gastroenterological specialists like yourselves should be especially appreciative of this system of expressing concentrations Let us take two values for chloride ion for comparison, 100 mEq/L (per liter of original blood plasma rather than per liter of water), and 150m Eq/L (per liter of gastric juice) The following equations furnish the simple conversions involved in changing from the frequently employed mg % (mg per 100 ml) to mEq/L and *vice versa*

For simplification and for convenience in the ensuing discussion, we will assume that the gastric fluid lost from the body during the day is a mixture of equal parts of the "active and of the "resting' gastric juice Such a mixture will have the ionic composition shown in the middle diagram of the lower group This, of course, is an approximation, although entirely valid for purposes of discussion

(2) *The Reflection of the Large Loss of Gastric Fluid in the Altered Composition of the Blood Plasma* Attention may now be directed to the lower group of three ionic diagrams in the figure On the left is the pattern of normal blood plasma, pH 7 4 On the right is the abnormal pattern of blood plasma, now pH 7 6, which has resulted, after the breakdown of compensating and protective mechanisms, from the unrelieved loss of acid gastric juice by pernicious vomiting Between the two is the pattern of the fluid lost Of course we are not dealing with a literal subtraction of the pattern of the fluid lost from that of the original plasma pattern, yielding the final abnormal plasma pattern, since ionic diagrams show only concentrations and furnish no idea of the volumes involved in the process We shall return to this point, essential for full understanding, and of importance as a guide to the amount of replacement therapy required In the ionic diagram on the right, 6 arrows point to 6 different areas in the abnormal plasma diagram, which will be taken up systematically

(a) Elements in Composition of the Normal Plasma It may not be amiss to say a few words about the ionic composition of normal plasma First, we may note that, as has been said, Na^+ is the predominant cation of extracellular fluid It occupies a space on the diagram equivalent to 91 per cent ((146 × 100)/160) of the total cations The little open space on the bottom houses the Ca^{++} (approximately 5 mEq/L_{H_2O}), Mg^{++} (approximately 3 mEq/L_{H_2O}) and K^+ (about 6 mEq/L_{H_2O}) The concentration of potassium in extracellular fluids is very low, and the ratio on a molar equivalent basis, of Na^+/K^+ is 24/1, and is quite zealously maintained probably by hormonal homeostatic control, operating on the kidneys, tissues, etc Departures from such maintenance of sodium to potassium in extracellular fluid are well recognized in Addison s disease, where the ratio of Na^+/K^+ falls, and in familial periodic paralysis, in which the ratio periodically increases In intracellular fluid, on the other hand, owing to the dominant position of K^+, the ratio of Na^+/K^+ is very different from that in blood pla ma In the intracellular fluid of skeletal muscles, for example, Na^+/K^+ = (12 mEq/L_{H_2O})/(137 mEq/L_{H_2O}) = 0 09 (based on analyses of Hastings et al, corrected for presence of an extracellular phase in the tissue) In comparison with blood plasma, information upon the composition of intracellular fluids is scanty At present, what information we have is of questionable reliability and somewhat difficult of interpretation owing to uncertainty as to how much of the fluid in various tissues represents true intracellular fluid, and how much is 'trapped extracellular fluid However, it is recognized that, with tissue breakdown in dehydration states, one may expect some deficit in tissue potassium, which may be designated as *potassium cytopenia*, in distinction to

reduced K^+ in blood plasma *hypopotassemia* or *hypokaliemia* Hypopotassemia may accompany potassium cytopenia, but, more often in untreated frank dehydration, there may actually be an elevation in the concentration of serum K^+, despite the impoverishment of this ion in intracellular fluid (see later)

Certain features on the anionic side are of particular interest First, the bicarbonate anion, HCO_3^- forms about one fifth, in comparison with Cl^- which is three-fifths of the total anions of blood plasma The HCO_3^- is a measure of the *alkaline reserve* (Van Slyke and Cullen) which is that fraction of the total cations or fixed base of the type of Na^+, which is associated with or subtends or balances the HCO_3^- Bicarbonate is the most labile anion of blood plasma and of extracellular fluids It is the anion of the weakest acid (carbon dioxide or carbonic acid) present in measurable amounts in blood plasma, and hence bicarbonate readily reacts with any stronger acids which may momentarily in metabolism invade the blood Thus the measurement of HCO_3^- concentration affords an index of departure from normal acid base balance *The bicarbonate goes down in acidosis up in alkalosis* Not shown in the diagram is the concentration of free CO which represents the amount of carbonic acid, H_2CO_3 in blood plasma The amount, under normal conditions is one twentieth of that of the bicarbonate anion You are doubtless, more familiar with the expression volumes per cent of CO the *carbon dioxide content*, as a measure of the *alkaline reserve* of the plasma This is an illustration of some of the inconsistencies of notation to which we have become inured, but which for clear thinking it is desirable to avoid The CO_2 content is determined by the familiar gasometric procedure in which by means of added acid all of the bicarbonate is converted to CO_2 For example, per liter of blood plasma there are actually present 26 mEq/L of HCO_3^- and only 1 3 mEq/L of free CO_2 In the analysis the bicarbonate is converted into CO and therefore we express in volumes of gas some thing 95 per cent of which in blood is not a gas at all but an inorganic anion To convert 26 mEq/L of HCO_3^- into volumes per cent (ml per 100 ml) of CO the gas factor 2 24 (derived from 22 400 ml the volume occupied by 1 mol of a gas under standard conditions of pressure and temperature) is used 26 mEq/L × 2 24 = 58 3 vol % CO_2 which represents bicarbonate In the same way 1 3 mEq/L × 2 24 = 2 9 vol % (the actual free CO) Now 58 3 + 2 9 = 61 2 vol % the familiar normal value for the total CO content

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$$\text{mEq/L} = \frac{\text{mg } \% \times 10 \times \text{valence}}{\text{atomic weight}} \qquad (1)$$

$$\text{mg } \% = \frac{(\text{mEq/L}) \times \text{atomic weight}}{10 \times \text{valence}} \qquad (2)$$

For chloride the valence is 1, the atomic weight is 35 5, and the factor 10 is to adjust from a volume of 1 liter (1000 ml) to 100 ml Using equation 2, the plasma Cl^- concentration of 100 mEq/L is found equal to 355 mg %, while the gastric fluid Cl^- concentration of 150 mEq/L is 50 per cent greater, and is equal to 532 mg % Except for the advantages of the milliequivalent expression, which have been mentioned already, in these particular cases, no ambiguity need arise in the use of either concentration term This is so, since each refers specifically to the concentration of a single ion, Cl^- However, unfortunately and inexcusably, an outmoded practice still persists of giving concentrations in mg %, not of chloride, Cl^-, but of sodium chloride, NaCl Thus, using the molecular weight of 58 5 (for NaCl), rather than the atomic weight of 35 5 (for Cl^-), by substitution in the same equation 2, one obtains (from the milliequivalent values for Cl^-) the respective values of 585 mg % for plasma NaCl and 878 mg % for gastric fluid NaCl Aside from the fact that there is no reality to the existence in solution of NaCl as such, it should be obvious to all, and especially to gastroenterologists, that the value of 878 mg % of NaCl in gastric fluid is not only misleading, but completely fictitious Reference to the center diagram of the lower group in the figure verifies the well known fact that most of the Cl^- in gastric fluid represents not NaCl at all, but HCl We may close this sermon with Sufficient unto the day is the good thereof"

To complete the tally of anionic components, there is a space of only 7 mEq/L $_{H_2O}$ devoted to the combined ions of phosphate, $HPO_4^=$, sulfate, $SO_4^=$, and the anions of organic acids as lactate, beta hydroxybutyrate, etc Finally, there is a space of 18 mEq/L$_{H_2O}$ occupied by proteinates, the anions of the plasma proteins The 18 mEq/L$_{H_2O}$ correspond to 7 5 gm of proteins per 100 ml of plasma water, or to 7 0 gm per 100 ml of plasma These non diffusible plasma constituents are responsible for the phenomenon of colloid osmotic or oncotic pressure (COP), operative in fluid exchange across capillary membranes, and important in theories of edema formation in hypoproteinemic states However, COP is practically negligible, less than 1 per cent of the total osmotic pressure If one summates the total positive and total negative ions in blood plasma, the value of 320 mEq/L$_{H_2O}$ is obtained (from 160 mEq/L$_{H_2O}$ each of cations and anions) Since a very large proportion of the ions are univalent, this summational value approximates the molar concentration responsible for the total osmotic pressure of blood plasma, but does not evaluate it exactly To get the total osmotic concentration one must convert the 320 mEq/L$_{H_2O}$ into osmotic mEq/L$_{H_2O}$ This is done by correcting for the presence of bivalent ions (Ca^{++}, Mg^{++}, $HPO_4^=$, and $SO_4^=$), whose corresponding mEq values are divided by 2, and

for polyvalent ions (the proteinates⁼), whose mEq value of 18 is divided by 8, the effective valence of these complex ions In this way, 320 mEq/LH_2O is converted into 308 osmotic mEq/LH_2O, or, as it is more usually designated, 308 milliosmolar, or 308 mOsM/LH_2O Now, 308 mOsM/LH_2O is the same as 0 308 osmolar, or 0 308 OsM/LH_2O Let us consider the salt NaCl, which in solution will dissociate into two osmotically active particles A solution of NaCl which will be *iso osmotic* (possessing the same osmotic effect) with the total osmolar concentration in blood plasma must be in normal terms ½ of 0.308, or 0 154 Thus a 0 154 normal (0 154 N) solution of NaCl is *iso-osmotic* and also *isotonic* with blood plasma The molecular weight of NaCl is 58 5 58 5 × 0 154 = 9 0 gm /L = 0 9 gm /100 ml = 0 9 per cent This is the actual method used to derive the familiar latter value On the other hand the isotonic concentration of a non ionizable substance, like glucose is 0 308 molar (equivalent to 5 5 per cent) Isotonic repair solutions of all ionizable univalent salts must have the same normality of 0 154 N/L Is it not much easier to remember this single value than the following assortment sodium chloride, 0 9%, sodium bicarbonate 1 3% sodium lactate, 1 73%, potassium chloride 1 15%?

(b) Composition of the Plasma in the Deficit State The right lower ionic diagram of the altered blood plasma reflects the body deficits of salts (osmotic factors) and water, which have resulted from the loss of osmotic factors and water through the unrelieved vomiting The altered ionic composition points also the character of the ionic disturbance, incident to the loss of a fluid of acid pattern (gastric juice) Furthermore, there is evidence, as will be seen, of (a) an attending element of starvation (b) functional renal impairment and (c) inspissation or dehydration of the blood A quick glance at this diagram discloses at once two main features There is a shrinkage or contraction of the total concentration And, more strikingly there is a remarkable rearrangement especially on the anionic side of the individual ionic concentrations Here we find a marked shrinkage in the space devoted to Cl^-, but an actual expansion of the concentration spaces of all the other negative ions We will now proceed briefly and consecutively with some of the points towards which the arrows are directed from the top down (Fig 231)

(*1*) Deficiency of Osmotic Factors The top arrow points to the decrease in total ionic concentration At the face value the reduction from 160 to 145 mEq/LH_2O does not appear very large but this question is pertinent *How well does the blood plasma reflect the degree or extent of the body s salt deficit?* This amount of change in the plasma s total ionic concentration is of serious import, since the composition of the vascular fluid is protected against change Thus even a small change in the plasma is indicative of a breakdown or failure in protective devices (see below) It may again be emphasized that loss of water automatically accompanies loss of osmotic factors The decrease in plasma total ionic concentration goes hand in hand with *hypovolemia* (decrease in plasma volume)

(*2*) Expansion in Plasma Bicarbonate or Alkaline Reserve *Alkalosis* The

second arrow points to the HCO_3^- concentration of 59 mEq/L, corresponding to a CO_2 content of approximately 130 vol % This indicates "alkalosis," and is a direct consequence of the primary loss of "fixed" acid in the gastric fluid The alkalosis is of very severe grade, but more extreme alkalosis may be met with Dr Zintel and associates have reported a patient with Wangensteen drainage who had (before heroic therapy with ammonium chloride) a CO_2 content, as I remember, of 152 vol % (68 mEq/L of HCO_3^-) Their case is some sort of record

(3) *Hypochloremia* The third arrow is directed towards the much contracted Cl^- concentration space This, again, is a direct consequence of the ionic pattern of the fluid lost from the body It may be mentioned, at this point, that hypochloremia will also be present after large loss of alkaline intestinal fluids in severe diarrheas Indeed, the alterations in the ionic diagram of the plasma would be rather similar to those shown here, with the exception of HCO_3^-, which would be less than normal (reflecting "acidosis")

(4) *Kidney Disability,* Starvation Ketosis Attention is next directed to the expansion of $HPO_4^=$, $SO_4^=$, and organic acids (beta hydroxybutyrate$^-$) from the normal value of 7 to that of 17 mEq/L_{H_2O} The excretion of these anions and their corresponding acids is the exclusive function of the kidneys *The increase in $HPO_4^=$ and $SO_4^=$ is, hence, a direct reflection of a progressively developing renal disability* Larger increases in the concentrations of these ions may occur in renal acidosis To a certain extent, plasma Cl^- and HCO_3^- tend to change in opposite directions, as if a decrease in one is compensated by an increase in the other However, the increase in $HPO_4^=$ and $SO_4^=$ should not be regarded as compensatory for the decrease in Cl^- If the kidneys were functioning normally, the concentration of the bivalent anions would not have changed significantly In the dehydration state, oliguria or, indeed, anuria (complete renal shutdown) may be present Perhaps the primary objective of therapy should be to restore some degree of kidney function A word must be said about the cation, potassium, whose concentration is not adequately suggested because of the small size of the open space at the bottom of the ionic diagram K^+ may be slightly decreased, in proportion to the decrease in Na^+ On the other hand, two factors appear to operate to produce a more frequently found increase in plasma K^+ in dehydration in pyloric obstruction (a) Increased cellular destruction, which accompanies dehydration, probably "liberates" intracellular K^+ (b) The excretion of this liberated K^+ is not normal, owing to renal disability We have here the paradoxical, albeit logically explainable, situation of body potassium deficit (potassium cytopenia) and hyperpotassemia *It is this very type of patient to whom one dare not administer potassium replacement therapy, before good kidney function (active urine flow) has been restored!*

The increase in ketone bodies (beta hydroxybutyrate$^-$ and acetoacetate$^-$) in the plasma is indicative of the fact that the element of starvation ketosis has entered the picture The extent to which the presence of these anions of organic acids "spares" the bicarbonate anion may be taken as a measure of the effectiveness of this agency in combating the alkalosis The very fact that severe alkalosis still exists, despite the ketonemia speaks for itself

There are instances, however, to which attention has already been called, in which the element of starvation ketosis may be of sufficient magnitude to mask or modify the picture of frank alkalosis

(5) *Anhydremia* The fifth arrow points to one of the gravest alterations of the plasma in the dehydration state The change from the normal level of plasma proteins of 18 mEq/L H_2O to 23 mEq/L H_2O corresponds to a change from 7 gm % in the original normal plasma to about 9 gm % The large protein molecules are essentially non-diffusible and, therefore, an increase in the concentration of this item reflects the inspissation or dehydration of the blood the condition of *anhydremia* The hypovolemia (reduction in plasma volume) is also reflected in hemoconcentration which can be measured or deduced from a relative increase in the concentration of hemoglobin The increased viscidity of the blood (in hemoconcentration) interferes with normal circulatory dynamics—a factor of the utmost importance in the dehydration state This factor may be implicated with some responsibility for increased tissue breakdown as well as for progressive disturbance in renal function With reference to the increase in plasma proteins two other points may be emphasized *The colloid osmotic pressure has been increased*, so that the inference could be drawn that this operates as a protective device against the decrease in total osmotic factors However, it may be recalled that the plasma proteins exert less than 1 per cent of the total osmotic influence and hence as a compensatory mechanism, their increased concentration is a wholly inadequate gesture There are no good portents in this elevation above normal in plasma protein concentration Also, as will be seen the high value for plasma protein may mask the existence of an actual body protein deficit

(6) Uncompensated Alkalosis The bottom arrow is directed towards the independently determined plasma pH of 7 6 This more directly than the elevated plasma bicarbonate (representing the alkaline reserve) is indicative of severe alkalosis Furthermore, the departure from the normal pH means that the alkalosis is *uncompensated* Time does not permit an adequate discussion of this phase of the problem In a developing disturbance in the body s acid base equilibrium respiratory compensation is an important factor In contrast with hyperpnea associated with acidosis alkalosis is usually accompanied by shallow breathing This is an attempt to keep in more CO_2 (really carbonic acid H_2CO_3) a desperate effort to try to maintain as close to normal as possible the buffer ratio of $[HCO_3]^-/[CO_2]$ in the face of an enlarging $[HCO_3]^-$ The rule is that compensation' in such a developing state is never perfect and invariably results in uncompensation So long as the ratio of $[HCO_3]^-/[CO_2]$ and that of other buffer pairs is kept close to normal the pH will not be changed markedly Barcroft has described the blood buffers as mechanisms of evasion They function in emergency final adjustment depends on the lungs and, especially the kidneys The pH of 7 6 indicates that the capacity of the protective devices of acid base maintenance has been exceeded Help, from the outside is called for

The pH of 7 6 is at the tetany level and yet most individuals in this critical state of alkalosis and dehydration of acute pyloric obstruction rarely exhibit

frank tetany However, it is known that severely hypochloremic patients of this type may be thrown into tetany, if subjected to excitement

(7) *Hyperazotemia* Not pictured in such diagrams of the plasma are the concentrations of the non-ionic constituents Among these, of greatest present interest is the non-protein nitrogen, N P N, or its largest moiety, the urea nitrogen, U N (The latter undergoes parallel changes with the former, and, in this instance, has similar interpretative significance) The term *hyperazotemia* refers specifically to an increase above normal of the non protein nitrogen of the plasma In such cases as we are discussing the increase may be twofold or greater Larger increases in N P N are encountered in and are most commonly associated with severe renal insufficiency This factor is, of course, also present here However, the consensus is that, in dehydration states, the more direct or primary cause of hyperazotemia is the accompanying increased cellular destruction (i e, breakdown of tissue protein) Kidney disability emphasizes the condition through retention of nitrogen The exact reasons for increased tissue protein catabolism are not well understood Such factors as tissue anoxia, owing to the disturbed circulatory dynamics, may be operative, or "toxic destruction of protein," comparable with that seen in febrile states, may be a factor It is most desirable not to regard the attending renal dysfunction as irreversible, but to direct early therapy towards improving renal flow As a rule, this can be accomplished in the first few hours by the institution of replacement therapy, designed to quickly overcome the hypovolemia (anhydremia), and thereby help the kidneys The best agents in this early aid to restoration of function remain sodium chloride and glucose (although blood plasma may be also considered), but *not potassium solutions* As soon as effective renal flow is established, a rapid return of the N P N towards normal may, in most cases, be expected

I would like to interject an issue here, though I know it is a little unfair, since time will hardly permit of debate I also know from past personal experience, when some of my own pet views were questioned, that nothing hurts more, or may elicit a more violent reaction, than to have someone step on your mental ingrown toenails However, it remains important to try to direct thought into productive channels I refer to a view which I have heard expressed that the hyperazotemia, particularly the increase in blood urea, operates as an osmotic protective mechanism The idea is that the expansion of the urea compensates for the contraction in total ions There can be no doubt whatever that urea exerts some osmotic effect, but it appears unrealistic and misdirectional to regard as beneficial or "protective" a pathologic situation, attained by means of tissue breakdown and kidney disability Moreover, urea cannot substitute for ions like Na^+ Cellular membranes appear to be so completely permeable to urea that it cannot function in the "retention" of water in body spaces

WHAT PLASMA CHEMISTRY MASKS OR FAILS TO DISCLOSE

No discussion of this subject can be regarded as even approximately complete without some word as to the limitations in the chemical findings,

collected in the ionic diagram of the altered blood plasma Allusion has been made already to the fact that the concentrations in the plasma do not serve to indicate the extent or severity of the body s deficits Two factors operate to prevent accurate reflection in the composition of the plasma (a) The composition of the plasma is not changed materially until protective mechanisms have become exhausted Among these omitting rigid arguments against blind faith in its operation is the interstitial fluid, whose volume is approximately three to four times greater than that of the blood plasma, and whose ionic composition is practically identical with the latter It is assumed that contractions and expansions in the interstitial fluid are better tolerated than volume changes in the plasma Depletion to near exhaustion of the interstitial fluid reserve precedes (and protects against) the alteration by depletion of the vascular fluid Besides, deficits in intracellular fluid have probably preceded the frank disclosure of the deficit state by the plasma (b) The dehydration of the blood (anhydremia) increasing the concentration per unit volume particularly of non-diffusible constituents, also operates to mask the true body state These factors cannot be disregarded in estimating on the basis of the composition of the plasma the amount of replacement therapy required Thus the total ionic concentration has been reduced at face value by only 15 mEq/L$_{H_2O}$ (from 160 to 145 mEq/L$_{H_2O}$) From this it may be calculated that the total plasma deficit (3 liter volume basis) of osmotic factors corresponds to that of only 450 to 500 ml of 0 9 per cent saline However, in view of the much larger volumes and proportionately larger depletions of the interstitial and intracellular fluids the body deficit may be taken as three times (a minimal estimate) and up to six times or more than that of the plasma deficit

The plasma proteins present in some respects a special case Here, the dehydration of the blood has resulted in an increase in protein per unit volume This hyperproteinemia may mask an actually existing tissue or total body protein deficit Potassium for other reasons already mentioned falls into a similar category

Certain biochemical aspects of acute pyloric obstruction have been discussed The prominent chemical alterations in this disease process have been dealt with systematically to illustrate how they contribute information essential in the total picture of the underlying derangement No time has been allotted to a detailed discussion of chemical therapy but the direction of proper therapy may have been suggested from the presentation of the functional dislocations (circulatory and renal) and deficits (osmotic factors and water) which have developed owing to the unrelieved loss from the body of the acid gastric fluid

THE CAUSE OF DEATH IN STRANGULATION OBSTRUCTION AN EXPERIMENTAL STUDY

PAUL NEMIR, JR , M D

I should just like to give a brief summary of the work done by Dr Hawthorne, Dr Drabkin and others of us in the Harrison Department of Surgical Re search and the Department of Physiological Chemistry of the University of Pennsylvania during the past eighteen months

We have studied the problem of strangulation obstruction, utilizing certain of the newer concepts of management By the intensive administration of blood, glucose, saline and gelatin we have demonstrated a significant though limited prolongation of the survival times of dogs having a strangulation obstruction By the methods used, we obtained an experimental animal in which hemorrhage, shock, dehydration, electrolyte imbalance and perfora tion of the loop with a generalized bacterial peritonitis were reasonably ex cluded as the cause of death and in which studies on the blood, peritoneal fluid and gut content could be made at will By our methods we prolonged the lives of animals sufficiently for factors other than those amenable to present methods of management to become manifest

Figure 232 shows the method which we used to produce the strangulation The bowel was severed at a distance approximately 150 cm from the liga ment of Treitz, and both ends were turned in Fifteen centimeters above the proximal turned-in end a 30 cm segment of gut was strangulated by doubly ligating the veins in the base of the mesentery and severing and ligating the communicating arteries and veins at either end of the strangulated segment Plastic and latex tubes were then placed in such a manner that we were enabled to withdraw peritoneal fluid and gut contents at will

We followed the chemical, bacteriologic and spectrophotometric changes that occurred in the gut lumen, the peritoneal fluid and the blood

It was shown that late in the course of strangulation obstruction, the bowel wall suddenly became permeable to its intraluminal contents, and this fluid passed out into the peritoneal cavity and thence into the blood stream This course of events was indicated by the sudden change in the character of the peritoneal fluid from a pink or strawberry colored, odorless, coagulable fluid to a reddish-black or black, foul smelling, non-coagulable fluid very similar in its physical and chemical properties to that found in the gut lumen

The change in the character of the peritoneal fluid was abrupt and striking A representative course was illustrated by one of the animals which died at thirty hours For a long period following strangulation, up until twenty-eight hours in this animal, the strawberry colored fluid was recovered from the peritoneal cavity The reddish black fluid was removed at twenty nine hours, and the black fluid was recovered from the peritoneal cavity just prior to the death of the animal

This color change was important in that we were thus enabled by spectro photometric studies to follow directly the course of events We demonstrated the presence of an abnormal pigment, a hemin or hemoglobin derivative hitherto unreported *in vivo*, present first in the gut lumen from around twelve hours onward, later in the peritoneal fluid after the color change was noted, and thence in the blood stream

In view of the rapid deterioration and death of the animal after the appear ance of the *black fluid in the peritoneal cavity*, *it appeared reasonable that*



Fig 232 Method of producing strangulation in experimental animal

some lethal factor was present in this late or black fluid Injections of both the early pink or strawberry colored fluid and the black fluid by both the intraperitoneal and intravenous routes into normal unanesthetized animals were therefore undertaken

Table 35 shows the results of our injection experiments It will be noted that death occurred in none of the six animals receiving the pink or straw berry colored fluid in very large amounts by either the intravenous or intra peritoneal routes On the other hand four of the seven animals receiving the

Table 35 Peritoneal Fluid Injected

RECIPI NT ANIMAL	WEIGHT (KG)	SOURCE	HRS BETWEEN STRANGULATION & WI HDRAWAL	CHARACTER OF FLUID	ORGANIS IS PRESENT	A IOUNT—TOT L CC	A IOUNT—CC /KG	METHOD	INTERV OF H S GIVEN	CO MENT
1	9 0	331	3½ 4	P k odo less c ag l ble	Hemo clostrid	400	45	I P	8	No ffect
	7 0	237	1 8	P k odo less o gulabl	H mo l tr d a B col S lmonell	340	50	I P	4	No ff ct
3	7 0	357	4 o l s	P k od l co g l ble	B oli Hemo trep	80	40	I P	2	No ff t
4	7 0	347	24 o le s	Pink dorless gulabl	Hemo clost d a B coli Non H mo st p No Hem clo t A ae ogenes	10	30	I V	2½	N eff t
5	6 7	295	4 o less	P k odo l o g l ble	B col H mo st p Non H mo st p	300	45	I V	3	No effect
6	8 5	365	0– 5	P nk odo l co gul ble	Hemo clost d a B li H mo st p Non Hemo strep A rog s	4 5	50	I V	1	No ff t
7	9 0	331	28 3 36 42	P k od l c g R dd sh black Bl ck f l n o g	H mo l tr d B col Str p vir d s	100 100 } 360 160	40	I P	3	No effect
8	10 0	235	8 32	Bl ck f ul n -c ag l ble	Hemo clo trid B coli H mo st ep Non Hemo trep Non Hemo clo t	350	35	I P	1½	D ed 6 hrs
9	10 0	357	35	Bl k fo l n n o gulabl	Hem cl t d a B oli Hemo st p Non Hemo st p N n Hemo cl t A og nes B p ot	350	35	I P	6	D d 7 h
10	7 3	357	35	Bl k fo l n n co gulabl		24	3	I V	At on	D d 5 hrs T = 107
11	5 5	347	9 30	R d bl k no -co g Bl k f l n co g	H mo lost d a H m t p N Hem tr p N n H mo lo t A og B p t	35 65 } 100	18	I V	2	D d 30–40 hrs T = 104 t 4½ hrs
1	8 0	365	8	R d bl k f int d n-c g	H mo lo t d B l	155	19	I V	2	N ff
13	8 3	165	8	R d bl k f od n-c g	H mo p A	125	15	I V	1	Died 5 d ys—D mpe ( ) T = 105 4½ h

reddish black or black fluid died within less than thirty hours after injection although they received much smaller amounts than those animals given the pink fluid

We have no evidence at hand to indicate that the abnormal pigment which was demonstrated is the toxic agent That it is in some way related to the toxicity of the late or black peritoneal fluid, however, is indicated by the fact that the most toxic fluid showed the greatest change in the spectral abnormality Also, as stated, the abnormal pigment was not found in the gut lumen until around twelve hours In view of the fact that less than twelve hour old strangulated gut contents have been injected into recipient animals without causing death, the relationship between the altered pigment and the toxicity seems evident

EFFECT OF VOMITING AND FLUID LOSS ON SERUM POTASSIUM VALUES CLINICAL AND ELECTRO-CARDIOGRAPHIC OBSERVATIONS

SAMUEL BELLET, M D

Following fluid loss by vomiting and diarrhea there results not only a loss of the sodium chloride and water from the extracellular fluid but also a disturbance in the intracellular ions as well Recently, the reports of Butler, Fenn Darrow Talbott, Gamble and others have called attention to the alterations in the intracellular as well as extracellular fluid which occur during alkalosis and the acidosis which accompanies loss of fluids from the body Darrow and others have shown that there is a marked loss of potas sium accompanying states associated with dehydration particularly diarrhea in infants Similar losses of potassium have also been shown to occur in other conditions to be discussed later

Scudder and his associates (1938) studied a series of 20 untreated cases of intestinal obstruction and found the serum potassium to be raised in 7, low in 5 and normal in 8 Recently Drs Nadler Gazes and myself have studied a series of 25 patients with vomiting due to intestinal obstruction The serum potassium was found to be low in all of these patients on admis sion That there was a lowering of the intracellular potassium in these cases is indicated by the fact that during the recovery stage they tended to retain a large proportion of the injected potassium for several days These patients were studied clinically electrocardiographically and chemically upon admis sion and at various stages during treatment As one would anticipate most of these patients were quite ill on admission They manifested varying degrees of dehydration through loss of fluid by vomiting and in addition in a few patients by diarrhea Mental symptoms ranging from disorientation

to coma were observed in some of these patients, and many presented the picture of shock at the time of admission to the hospital Operation was performed where possible to relieve the obstruction Parenteral fluids and electrolytes were administered prior to and following operation, as will be indicated

SERUM POTASSIUM AND OTHER ELECTROLYTE VALUES

The serum potassium on or soon after admission ranged between 2 3 and 2 5 mEq/liter in 8 patients and between 2 5 and 4 1 mEq/liter in 17 patients In general the level of the serum potassium varied with the degree of alkalosis, the greater the degree of alkalosis, the lower the serum potassium In practically all of these patients, the serum potassium dropped to still lower levels following parenteral therapy which did not include potassium

Of particular interest was the relationship between the level of the serum calcium and the serum potassium When the serum potassium values were *quite low (1 7 to 3 3 mEq/liter), usually associated with a considerable degree* of alkalosis, the serum calcium levels also tended to be low but not nearly so low proportionately as the serum potassium The serum calcium levels ranged between 3 5 to 4 5 mEq/liter in most of our patients when the serum potassium was low This decrease involved the ionizable as well as the un-ionizable fraction

FUNCTIONS OF POTASSIUM IN THE BODY

This electrolyte is intimately connected with the contractile process Potassium is essential for normal muscular function A low potassium results in weakness, poor muscle tone, *paralysis and ultimately death* Smith has observed that dogs which were fed on a diet low in potassium developed paralysis of various muscle groups, and, unless potassium was administered, a state of collapse and death Deficiency of body potassium has produced necrosis of heart muscle in the experimental animal

Potassium is essential also for normal nerve function, it is particularly concerned in the neuromuscular transmission of the impulse It also acts in *initiating the excitation process In addition potassium also* has a pressor effect which resembles that of epinephrine The pressor effect is the result of the following mechanisms a central action, a peripheral effect on blood vessels, a stimulating effect on epinephrine secretion, and probably an increase of muscle tone

Potassium is important for normal carbohydrate metabolism Fenn demonstrated that the deposition of glycogen in the liver could not take place unless accompanied by *a certain amount of potassium and water* He believes that this may be true for the deposition of glycogen in muscle as well as in the liver Several investigators have postulated that potassium is essential for the formation of phosphorylated carbohydrates within the muscle cell It has been presumed that it acts as a catalyst in such reactions promoting esterification of the inorganic phosphorus, the first step in the synthesis or breakdown of glycogen

The following cardiac effects during hypopotassemia have been noted dilatation of the heart, the development of systolic murmurs ectopic rhythms and profound electrocardiographic changes of a type associated with severe grades of myocardial abnormalities In addition, the blood pressure is usually low Such profound effects on the heart obviously add to the severity of the clinical picture These alterations are usually promptly reversed by the administration of potassium

RECOGNITION OF POTASSIUM DEFICIENCY

Low concentrations of potassium in the serum and diminution in cellular potassium have been observed in the following conditions (1) diminished intake of potassium, (2) in animals and patients treated with large doses of desoxycorticosterone (3) familial periodic paralysis, (4) diabetic acidosis (5) Cushing s syndrome (6) intestinal obstruction and (7) diarrhea

The diagnosis of potassium deficiency depends upon (a) recognition of the conditions likely to be associated with this disturbance as mentioned above, (b) the presence of muscular weakness and atonic muscles and occasionally muscular paralysis, (c) characteristic electrocardiographic changes which return to normal when potassium is given, (d) confirmation by chemical determination of the serum potassium Particularly important is an estimation of the loss of body potassium by measurement of the retention of this electrolyte during the state of recovery

In man hypopotassemia has been studied chiefly in familial periodic paralysis In these patients there has been noted muscle weakness, difficulty in respiration due to paralysis of the accessory muscles of respiration, general muscular paralysis and even death More recently, similar phenomena have been observed following therapy in diabetic acidosis and in chronic nephritis where the serum potassium level may be as low as 2 0 mEq/liter While marked degrees of muscular paralysis are relatively rare accompaniments to potassium deficiency, minor and moderate degrees of muscular weakness are not uncommon In a recent paper Huang and Mao[17] describe 11 cases of transient paralysis occurring in patients with cholera on the second to ninth day after hospital admission The paralysis was regarded as analogous to that developing in familial periodic paralysis, and responded dramatically to the intravenous injection of potassium chloride Unfortunately, the authors were unable to determine the level of serum potassium

While no instances of frank muscular paralysis were observed in cases of our series, varying grades of muscular weakness and asthenia were present These were in many instances improved following the administration of potassium It would appear that mild and moderate grades of muscular weakness and asthenia resulting from hypopotassemia are probably overlooked and attributed to the underlying clinical state

Since a deficiency of potassium affects many vital functions, and since the potassium is depleted in intestinal obstruction it seems very probable that some of the symptomatology of intestinal obstruction may be the result of a deficiency of potassium This is based on the following (a) the marked

depletion of this important electrolyte in a relatively short period of time following vomiting, (b) the presence of asthenia, weakness, low blood pressure and a shock like state which resembles in many aspects the syndrome of hypopotassemia, (c) the profound electrocardiographic changes (d) Finally the administration of potassium results in the improvement of the symptoms and signs with an almost immediate restoration of the electrocardiogram to normal

ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH LOW SERUM POTASSIUM

The electrocardiographic findings in hyperpotassemia are quite well established The characteristic tall, narrow T waves, often accompanied by some widening of the QRS complexes, are reversible and give way to normal waves as the hyperpotassemia becomes lowered toward normal The electrocardiographic alterations associated with a low serum potassium have received less study In 1937 Bellet and Dyer reported characteristic electrocardiographic changes in 23 patients after their emergence from diabetic acidosis These changes consisted of a lengthening of the Q-T interval, depression of the S-T segment, and in some instances, inversion of the T waves The relation of these changes to hypopotassemia was not established originally However, the relationship of characteristic electrocardiographic changes in hypopotassemia and in diabetic acidosis has been well established by the more recent studies of Holler,[16] Branning and Nicholson,[3] Martin and Wertman,[18] and Nadler, Bellet and Lanning [19]

Hypopotassemia as a cause of characteristic electrocardiographic changes was first established in studies of patients with familial periodic paralysis (1940–41) In addition, Thomson published records of a case of Addison's disease where hypopotassemia resulted from the administration of desoxycorticosterone acetate A similar case, but without serum potassium values, was published by Currens and White [6] Brown, Currens and Marchand[4] reported the occurrence of muscular paralysis in chronic nephritis in 2 patients which was attributed to potassium loss Serum potassium values were not determined Ellis reported the electrocardiograms of 4 prisoners of war suffering from severe malnutrition and diarrhea The electrocardiographic changes closely resembled those of low potassium although other factors were probably operative Treatment of these patients resulted in a return of the records to normal These observations indicate that in a number of conditions other than diabetic acidosis there are similar and characteristic electrocardiographic changes There is a good deal of evidence to indicate that these distinctive electrocardiographic changes seen in these varied conditions are the result of potassium deficiency and not of the many additional changes that are present

MECHANISM OF POTASSIUM LOSS THROUGH THE VOMITING PRODUCED BY INTESTINAL OBSTRUCTION

Potassium is lost in intestinal obstruction mainly through the direct loss of the electrolyte which is present in the stomach and intestinal secretions

The potassium is further depleted by Wangensteen suction and by therapy with parenteral fluid, saline and glucose Long-continued vomiting of stomach secretions results in a loss of intra and extracellular fluids which contain potassium, and in the loss of potassium contained in the gastrointestinal secretions Falconer observed that the vomitus contained five times the concentration of potassium that is present in the serum Frenkel has found the potassium in vomitus to be from 40 to 50 mg per 100 cc Austin and Gamman[1] observed that gastric juice contains two and one-half times as much potassium as is found in blood serum With loss of gastric secretions more chloride is lost than sodium with resulting production of alkalosis The excess of sodium in proportion to chloride in such states may go into the cell, displacing potassium which is eliminated

Loss of potassium may also result through procedures designed to treat the vomiting and certain other symptoms caused by intestinal obstruction Suction by the Wangensteen or Miller-Abbott tube results in a loss of considerable amounts of fluid which carries away with it considerable amounts of potassium The concentration of potassium is somewhat greater in the gastric than jejunal juice In addition in the alkalosis produced by gastric suction—since there is a greater loss of chloride than sodium as stated above—sodium tends to go into the cell, replacing potassium which is eliminated

During periods of inanition there is a considerable loss of nitrogen from the cells This also results in a loss of potassium which is present in the cells in a ratio of 2 gm of nitrogen to 1 mM of potassium

The parenteral administration of glucose tends to diminish the serum potassium by driving the potassium into the cells of the muscles and liver This is particularly apt to occur when the cellular potassium is low In addition, glucose tends to produce a transient depletion of salt and helps to eliminate potassium by stimulating diuresis On the other hand glucose has a sparing effect on protein loss which occurs when the patient is not taking food by mouth Since protein and potassium are present in the cell in the ratio of protein 2 gm to potassium 1 mM, the sparing action of glucose on protein would tend to prevent the loss of nitrogen and to this extent, to diminish potassium loss from the body

Tarail and Elkinton have shown that one of the major factors in the development of deficits of potassium in these patients appears to be the continued excretion of potassium by the kidney during periods of restricted ingestion of this ion They have shown in some patients losses of as much as 41 mEq per day in gastric secretions However usually more potassium is lost in the urine than in the gastrointestinal fluid More potassium appeared in the urine when the serum concentrations were low than when it was at higher levels In 4 of their patients less potassium was excreted during periods of high intake than during those of low intake

EFFECT OF ADMINISTRATION OF POTASSIUM

Potassium chloride in the form of a 1 14 per cent (isotonic solution) was administered intravenously in a dose of 500 to 1500 cc in a period of two to

six hours This electrolyte was also given by clysis and in a few instances by mouth Following the injection, the patients showed evidence of clinical im provement as manifested by diminished weakness and a sense of well being The blood pressure, usually low prior to injection, often rose 30 to 40 mm after potassium had been given The diastolic pressure usually increased more than the systolic The improvement was temporary unless the cause of the potassium deficit was removed or the patient began to take food by mouth

Following the injection of potassium, the electrocardiographic changes ob served during hypopotassemia tended to return to normal The degree of this return depended upon the amount of potassium given After the admin istration of this electrolyte, the electrocardiogram tended to return to its pre vious abnormal configuration, unless potassium continued to be administered or the patient began to take food by mouth

EFFECT OF ADMINISTRATION OF POTASSIUM ON ELECTROCARDIOGRAM OF HYPOPOTASSEMIA

Following the administration of potassium, the depression of the S T segments diminished, the T waves tended to become, or became, upright, and the Q-T segments were shortened in every case (Figs 233 and 234) The degree of return to normal depended upon the degree of hypopotassemia present prior to injection and the amount of the electrolyte administered When small doses of potassium were given (100 to 200 cc), only a partial return to normal occurred With larger doses, a complete return to normal tracing was observed Extrasystoles which were present in 5 cases with low potassium were abolished following administration of this electrolyte

The rise in the level of the serum potassium varied considerably In many instances there was a slight rise (0 2 to 0 4 mEq/liter) in serum potassium apparently indicating that a considerable amount of the injected electrolyte had gone into the cells * If this were not the case, the value of serum potas sium after injection would be much higher than the values obtained

The electrocardiographic improvement following the administration of po- tassium was temporary in some cases, in others some degree of improvement persisted In about one-half to three hours following administration, the changes tended to revert to their previous configuration, although in some instances some degree of improvement in the T waves and S-T segment was preserved The electrocardiogram returned to a permanent normal con- figuration when the patient was able to take food by mouth at which time the potassium levels were maintained at a normal level

THERAPEUTIC IMPLICATIONS

The above findings indicate that potassium should be included in the parenteral fluids used in those states associated with vomiting due to the deficit in potassium Darrow suggests that the solution used to replace the electrolyte deficit should contain sodium chloride, sodium bicarbonate and

* That a positive potassium balance occurred at this period was shown by balance studies in 2 cases

potassium chloride when acidosis is present In alkalosis, on the other hand, a solution containing sodium chloride and potassium chloride is indicated

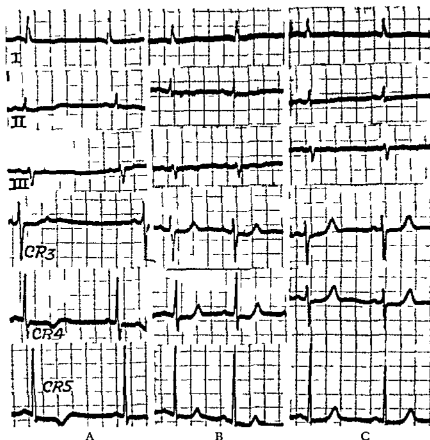


Fig 233 C L a white patient aged sixty six A electrocardiogram taken January 19 1948 after the patient had been vomiting four days Note inverted T wave in lead 1 ST depression with prominent U wave in lead 2 and lead 3 and inversion of the T wave in CR and CR with depression of the R T segment The serum potassium at this time was 2 85 mEq/L B after 250 cc of isotonic potassium chloride had been administered in a period of one hour and fifteen minutes Note flattening of the T wave in leads 1 and 2 Note that the T waves in CR_3, CR and CR are now upright C after 500 cc potassium chloride had been given in two and one half hours Note flattening of the T wave in lead 1 with a tendency to an upright configuration flattening of the T wave in lead 2 with upright T waves in CR CR and CR The potassium at this time was 4 08 mEq/L The blood pressure rose from the control value of 100/80 to 120/90 after administration of potassium chloride (Bellet et al in Am J Medicine Vol 6 June 1949)

The importance of establishing and maintaining a normal electrolyte balance cannot be overemphasized Potassium chloride may be given intravenously by clysis and by mouth The intravenous route can be used in patients who are

in some degree of shock and in the presence of diabetic acidosis In other instances, intravenous injection is usually associated with more or less severe pain at the injection site which renders its administration difficult Adminis

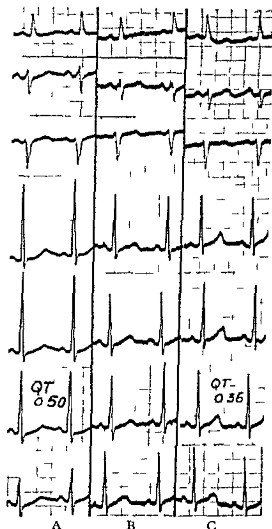


Fig 234 Case 10 Diagnosis pyloric obstruction with cyst of pancreas A control K = 2 7 mEq/L Note the low amplitude of the T waves in the precordial leads with lengthening of the Q T interval to 0 50 second B forty five minutes after 150 cc of 1 12 per cent potassium chloride had been given Note diminution of the RST segment depression with a slight increase in the amplitude of the T waves C two hours after 300 cc of potassium chloride had been given Note the further increase in the amplitude of the T wave The Q T interval now measures 0 236 second The serum potassium at this time was 4 3 mEq/L (Bellet et al in Am J Medicine Vol 6 June 1949)

tration by clysis is usually associated with no discomfort Administration by mouth can be resorted to where feasible, particularly when the patient has not been taking food by mouth

TOXICITY OF POTASSIUM

A discussion of toxic effects of potassium is of importance because the therapeutic indications are to supply potassium in large quantities to overcome the potassium deficit Potassium chloride has been given by mouth in doses from 5 to 15 gm with no untoward effect to patients with normal renal function Most of the potassium is eliminated in a period of three to four hours The toxicity following parenteral injection depends upon the rapidity and the amount injected the potassium level prior to injection, the renal function and probably the condition of the heart at the time of injection In man in absence of potassium deficit the maximum amount considered safe to inject intravenously at one dose is only 3 to 4 mg per kilogram of body weight The chief danger in the use of potassium salts is the production of serious cardiac abnormalities These develop when the extracellular concentration rises to a little more than twice the normal value If renal function is good potassium is rapidly excreted when the concentration in serum rises However rapid intravenous administration can exceed the rate of excretion Darrow has estimated that 3 5 mM of potassium or 0 26 gm of potassium chloride per kilogram is a safe dose if used with proper precautions The total dose should not be given in less than four hours and preferably should be given by slow drip in eight or more hours For parenteral administration he suggests its administration by hypodermoclysis since this method is safer than the intravenous route The administration of potassium chloride should be combined with sodium chloride or sodium chloride and sodium bicarbonate together with intravenous glucose in water sufficient to supply the water requirement The glucose probably facilitates the transfer of potassium to the cells

In the patients of our group all of whom had low levels of serum potassium and probably low cellular potassium we injected quantities from 500 to 1500 cc of a 1 14 per cent solution without untoward effect in a period of three to six hours Our experience would tend to indicate that patients in a depleted state of potassium can tolerate large quantities without untoward effects In case of doubt it is suggested that the injections be given slowly and frequent electrocardiographic checks be made before additional quantities are administered It is felt that the dangers of potassium intoxication have been considerably overrated

There are two conditions in which the administration of potassium might be dangerous (a) in the presence of renal damage and (b) in the presence of severe myocardial damage With renal azotemia a retention of potassium occurs in the body and may attain toxic levels in the serum The exact point at which the serum levels may be considered toxic or lethal has not been definitely determined in the human Deaths have been reported with serum concentrations of 8 mEq/liter but recovery has been reported when the concentration has been over 12 mEq/liter While we would consider that the presence of renal azotemia is an absolute contraindication to potassium administration, we are not so certain that the same is true in patients who have pre renal azotemia associated with a low serum potassium as is not infre

in some degree of shock and in the presence of diabetic acidosis In other instances, intravenous injection is usually associated with more or less severe pain at the injection site which renders its administration difficult Adminis

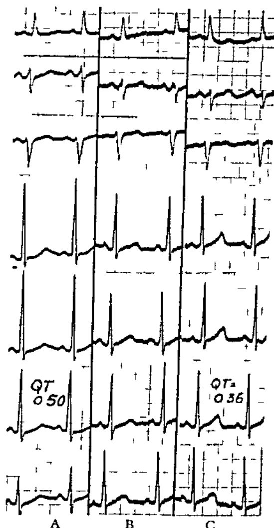


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PATHOLOGIC ASPECTS OF INTESTINAL OBSTRUCTION

WILLIAM E EHRICH, M D

The course of intestinal obstruction depends as is well known, on the tissue changes which develop in the intestinal wall There are two principal tissue changes that may be encountered one we may call the simple obstructional tissue changes, and the other the strangulated obstructional tissue changes

Simple obstructional tissue changes occur in simple obstruction such as mechanical obstruction or obstruction due to nervous imbalance Grossly we find distention of the proximal portion of the gut accumulation in the gut of fluid in acute obstruction and in chronic obstruction hypertrophy of the intestinal wall These two changes are of considerable diagnostic importance at the autopsy table

The microscopic changes in acute simple obstruction depend on whether

quently observed in dehydration states In such patients, the administration of potassium cautiously may be of help

It has recently been shown in our laboratory that the toxic level of serum potassium is modified by the cardiac state In dogs with severe grades of acut myocardial infarction, the toxic levels and the serum level at death were significantly below that observed in normal control animals or where the degree of myocardial infarction was slight or in a healed state

SUMMARY

In summary, it may be stated that the serum potassium is usually found to be low in patients with acute intestinal obstruction This is due to loss of this electrolyte in vomitus, lack of intake and loss in the urine The deple tion of potassium is increased by the administration of parenteral fluids which do not contain potassium, and by Wangensteen suction The electrocardiogram is a useful method in helping to confirm the presence of hypopotas semia and is a rough guide for estimating the increase of potassium in the serum following the administration of this electrolyte The administration of potassium resulted in a clinical improvement of the patient and the return of the electrocardiogram to normal The possible toxic effects of its adminis tration and the methods by which this may be avoided are discussed

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could pass through these spaces and eventually reach the peritoneum and cause peritonitis

Finally, a word about the *cause of death* in intestinal obstruction In high obstruction, death may be due to loss of electrolytes In strangulated obstruction or closed simple obstruction the patient may die from shock due to loss of plasma loss of blood resorption of toxic substances peritonitis and other changes In open simple obstruction, however, death cannot be explained this way, but we should consider other mechanisms It is possible that some patients die from an alarm reaction Others apparently die from cardiac or circulatory failure brought about directly or through a reflex mechanism by the general upheaval produced by the obstruction

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PRINCIPLES OF MANAGEMENT OF INTESTINAL OBSTRUCTION

HAROLD A ZINTEL, M D

Surgeons are deeply concerned with the physiologic disturbances resulting from intestinal obstruction In certain patients the recognition estimation of the degree and correction of these abnormalities of function may be of such importance that they may be largely responsible for the recovery or death of the patient Although the patient with complete obstruction cannot survive without operation the technical aspects of such an operation may be overshadowed by the associated physiologic problems In the history of medicine the morbidity and mortality of intestinal obstruction have been such as to lead many to conclude that there must be a toxic element associated with intestinal obstruction As the knowledge regarding the adverse effects of disturbances in fluid electrolyte and nutrition has advanced less and less has been heard of the possibility of a toxic factor per se

PREOPERATIVE TREATMENT

One of our major problems in preparing these patients for operation is the treatment of acute serum protein depletion It is well known that acute intestinal obstruction can produce a marked loss of circulating serum protein There is loss of serum protein into the lumen of the intestine and into the peritoneal cavity The serum protein level as determined in the laboratory is not an accurate index of the amount of protein lost At the risk of repeating something that has already been demonstrated this morning I would like to emphasize this point by citing a patient with a history of partial intestinal

or not the affected loop is open or closed If the loop is open, the pressure within the gut remains low Wangensteen found pressures ranging from 4 to 14 cm of water which is considerably less than the capillary pressure Consequently, there is little interference with the capillary circulation

On the other hand, if the loop is closed, if we have an obstruction of the colon, for instance, and there is competency of the ileocecal valve, then the pressure within the loop may rise up to 40 or 50 cm of water and thus approach the capillary pressure In this event, the circulation in the intestinal wall may come to a standstill, and there may be ischemia and anoxia followed by necrosis As a result, the gut may lose its viability, toxins and bacteria may permeate, and peritonitis may ensue

Strangulated obstructional tissue changes occur in incarcerated hernias, in volvulus and in intussusception In these cases the gut is dusky-cyanotic to bluish-black in color, the lumen contains a bloody material, and there may be a serosanguineous exudate in the peritoneal cavity Microscopically we find necrosis and infiltration with erythrocytes

It is obvious that these tissue changes are due to impairment of the circulation As a result of the strangulation, venous return is arrested, while arterial blood continues to enter into the strangulated gut This leads to anoxia, there is an increase in the permeability of the capillaries, erythrocytes escape into the tissue and necrosis develops As a result of these changes the gut loses its viability, toxins and bacteria may pass through its wall, and peritonitis may follow

This mechanism is obviously involved also in mesenteric thrombosis due to the thrombophlebitis following appendicitis or other inflammatory processes Again blood enters from the arterial side, but it cannot leave because the veins are obstructed by thrombi

In the more common type of so-called mesenteric thrombosis, we find, not thrombosis of the veins, but embolic obstruction of the arteries In these cases we observe true infarction which resembles strangulation in that the necrotic area is infiltrated with blood cells but differs in that the erythrocytes arrive there through collaterals instead of the supplying artery

Among the sequels of intestinal obstruction, *peritonitis* is of special interest It is easy to understand why strangulation should lead to this complication It is obvious that the resulting necrosis should permit bacteria to pass through the intestinal wall In simple obstruction, however, we have no necrosis, and yet peritonitis may occur

It is interesting that Wangensteen, in experimental simple obstruction in dogs, was able to demonstrate the presence of bacteria in the peritoneal cavity three to four and a half hours after initiation of the experiment It thus appears that bacteria can pass through the living intestinal wall The explanation of this phenomenon may be found in the edematous changes associated with simple obstruction It is now believed that connective tissue consists of a gel of hyaluronic acid and of fibers, there is no free fluid in normal connective tissue In the case of edema, however, spaces and channels containing free fluid make their appearance It is conceivable that bacteria

could pass through these spaces and eventually reach the peritoneum and cause peritonitis

Finally, a word about the *cause of death* in intestinal obstruction In high obstruction, death may be due to loss of electrolytes In strangulated obstruction or closed simple obstruction the patient may die from shock due to loss of plasma loss of blood, resorption of toxic substances, peritonitis and other changes In open simple obstruction, however, death cannot be explained this way, but we should consider other mechanisms It is possible that some patients die from an alarm reaction Others apparently die from cardiac or circulatory failure brought about directly or through a reflex mechanism by the general upheaval produced by the obstruction.

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obstruction of six days' *duration* Vomiting was not a prominent part of his history until the day before admission to the hospital During the first two days of hospitalization he was adequately hydrated judging by the fact that he had from 1000 to 1500 cc of urine per day At this time his hemoglobin was found to be 77 per cent, hematocrit 44 2 per cent and serum protein 6 2 gm per 100 cc One would be inclined to conclude that the patient was a satisfactory surgical risk in respect to the items mentioned The determination of the blood volume in this patient, however, showed that he was a poor candidate for any extensive surgery The expected total blood volume for this patient was estimated to be 6930 cc whereas his actual blood volume was 4059 cc If his total circulating serum protein and red blood cell mass were distributed in his expected normal blood volume, the hemoglobin then would be 45 per cent, the hematocrit would be 25 9 per cent and the serum protein value would be 3 6 gm per 100 cc If one were presented with these figures, one would hesitate to say the patient s condition was satisfactory for anesthesia and major surgery Such a patient should *receive massive blood* transfusions immediately before operation

I realize that the determination of the blood volume is not now an exact method and that there is a modest margin of error in such determinations This, *however, does not mean that the determination of the blood volume is* not useful clinically It may not be stretching the point to say that the determination of the blood volume is probably as accurate as the determination of the hemoglobin level or the determination of the blood pressure of a hypertensive patient

The blood volumes as determined by Walker at the Hospital of the University of Pennsylvania are performed by a modification of the Evans blue technic [1] In this method three blood specimens instead of one are taken after the dye has been injected *With the three blood specimens it is possible to* determine the rate of escape of the dye from the vascular system for each patient and thus calculate more accurately the blood volume of each patient Values obtained by this modification of the Evans blue technic, although not absolutely accurate, may be exceedingly useful clinically and may provide information which if used may lead to a marked reduction in morbidity and mortality of major surgical procedures Patients with obvious protein deficiency and weight loss secondary to chronically infected wounds did not have edema or apparent anemia and the clinical course of these patients, according to Lyons and Mayerson,[2] was characterized by a diminished tolerance for surgical blood loss, delayed healing of wounds and retarded convalescence They found that the quantity of blood necessary to restore total circulating red cell mass to standard values in patients with protein depletion uncomplicated by hemorrhage averaged 2700 cc , administered at the rate of 1000 cc per day

In regard to fluid and electrolyte balance, we do not administer sodium chloride solutions to patients unless there is a demonstrated need for sodium or chloride by determination of these elements in the blood The only time that even small amounts of sodium chloride solutions are used routinely in

the operating rooms of the Hospital of the University of Pennsylvania is in starting a blood transfusion Previously it was thought that during the operative period, patients needed additional amounts of sodium chloride and that any excess of sodium or chloride ions so administered would be selectively excreted Coller et al [3] have recently shown that excessive amounts of sodium chloride and water are, to a large extent, retained during the operative and immediate postoperative periods When a chloride deficit exists as determined by chemical analysis of the urine or blood serum sodium chloride solutions are administered More recently we have begun to use solutions containing potassium when there is chemical evidence of a deficiency of this substance With the flame photometer it is now a relatively simple matter to determine potassium levels in the blood and plasma

EARLY OPERATION vs INTUBATION

Many years ago Sir Arbuthnot Lane said Never let the sun rise or set on a patient with intestinal obstruction This dictum resulted in a marked reduction in mortality In reality Sir Arbuthnot Lane was advocating operating before marked physiologic disturbances developed However the mortality of 30 per cent[4] was still very high With modern supportive therapy and decompression the mortality of intestinal obstruction is now approximately 10 per cent [5]

Early operation is still the treatment of choice in the patient with typical signs of intestinal obstruction and with no associated clinical evidences of physiologic imbalance A patient with a history of vomiting of a few hours duration, absence of flatus and bowel movements distention and x-ray evidence of small intestinal obstruction should be operated upon promptly Intravenous fluids whole blood or plasma and introduction of a long tube such as the Miller Abbott tube are initiated before operation, but the operation is not materially delayed Also patients with obstruction obviously due to an incarcerated hernia or patients with evidences of strangulation of the gut should receive vigorous supportive therapy if necessary but should be operated upon with a minimum of delay The adverse effects of necrosis of the intestine may far outweigh any advantages the use of the Miller Abbott tube might have The point that I wish to make is this *The patient with obvious intestinal obstruction should receive adequate supportive therapy of course, but in the absence of clinical evidences of protein d pletion or fluid and electrolyte imbalance should not have the operation delayed just to have a Miller Abbott tube well down in the small intestine* The necessity of immediate operation when strangulation of the intestine is present or likely to develop needs no further comment

The patient with small intestinal obstruction of more than a few hours duration with a rapid weak pulse and clinical evidences of dehydration and hypochloremia on the other hand can usually be greatly benefited by the use of the Miller-Abbott tube and vigorous supportive therapy The chances of such a patient s surviving anesthesia and major operation without such treatment are not as good as when such therapy has been initiated The use

of intravenous fluids, sodium chloride, whole blood and the Miller Abbott tube should be continued until the physiologic conditions have been restored to normal or nearly normal levels

I would like to emphasize the protein loss of patients with intestinal obstruction by telling you of an experience we had not long ago At the time of operation the cause of intestinal obstruction was found to be a long fibrous band adherent to the peritoneal surfaces After division of this band, there was some question of the viability of a segment of the bowel approximately $\frac{1}{6}$ inch in length In an attempt to determine the viability of the bowel we used fluorescein intravenously and ultraviolet light While we were observing the circulation of the segment of bowel as indicated by the yellow color of the fluorescein in the vessels of the bowel, we noticed that our gloved fingers also appeared to be yellow With further observation the yellow color appeared on the surface of the large bowel where the bowel had been traumatized by simple, and we thought, gentle handling The fluorescein was observed to exude from the bowel, to be sure very slowly, but sufficiently to stain the sponges and to cause some small puddles of fluorescein stained material to collect in the sponges This demonstrated that trauma to the bowel could cause considerable exudation from the intact surface of the bowel wall

Before I say a word about obstruction of the large intestine I would like to say a few words about the use of long intestinal tubes Any such tube should be checked for patency or other mechanical defects before it is inserted into the stomach The tubing and balloon should be air tight and all connections should be sealed Time taken to insure adequate mechanical function of the tube before it is used may save a great deal of subsequent grief Once the tube is inserted *if it cannot be made to function properly within a reasonable period of time it should be removed*, and likewise "*If the tube appears to be functioning properly and the patient is not improving clinically, the use of the long tube should be abandoned* When a long intestinal tube does not function properly or does not produce clinical evidences of improvement, a short tube such as a Levin tube should be used Wangensteen[6] demonstrated that such a tube with the tip in the stomach and with constant suction will quite often produce satisfactory decompression of a considerable segment of the small intestine as well as decompression of the stomach

DECOMPRESSION OF OBSTRUCTED COLON

In regard to complete obstruction of the large intestine, the treatment of choice is a transverse colostomy Such a procedure will provide adequate and immediate decompression of the bowel Cecostomy (still preferred by many surgeons) is a simple procedure, it is not very traumatic, and in the majority of patients it will function satisfactorily However, for some reason, in some patients a cecostomy does not decompress the bowel and cannot be made to function properly The mortality following cecostomy a few years ago in many large clinics was 10 per cent That is a greater mortality than observed in all types of large bowel surgery at the Hospital of the University of Penn

sylvania I would strongly advise transverse colostomy if adequate and immediate decompression of the large bowel is to be achieved A long intestinal tube should never be used to decompress the large intestine for in approximately 75 per cent of the patients with obstruction of the large intestine the ileocecal valve is so tightly closed that decompression of the colon cannot be affected with a long tube

SUMMARY

In summary, the physiologic disturbances associated with intestinal obstruction may vitally influence the outcome of operation The problems in restoring and maintaining normal or nearly normal physiologic relationships may overshadow the technic of operation in patients with intestinal obstruction of more than a few hours duration Patients who do not have evidences of marked physiologic disturbances patients with incarcerated hernia, and patients with evidence of strangulation of the bowel should be operated upon without delay but with adequate supportive treatment Patients with small intestinal obstruction of more than a few hours duration, who show evidences of dehydration, hypochloremia and possibly peripheral vascular collapse, should be treated with long intestinal tube suction drainage and vigorous supportive therapy until they are better able to withstand anesthesia and operation Complete obstruction of the large intestine is relieved most promptly and satisfactorily by transverse colostomy

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PANEL DISCUSSION

Question In the examples of alkalosis given how much of what repair solution would be used to correct electrolyte imbalance? If there is renal damage how will chloride deficiency be corrected without causing an excess in sodium ion?

DR DRABKIN I shall try to answer the last question first As you recall, in the typical case of acute pyloric obstruction which we described, the oliguria or renal shutdown was regarded as a *reversible process* In most of these cases it may be assumed that kidney damage has not been overly serious, that renal impairment is not absolute One may think of replacement therapy in such circumstances as divided into stages The *first stage* of therapy is instituted promptly by the administration, to start with, of 500 to 1000 ml of 0 9 per cent (or 0 154 N) NaCl and about 1000 ml of hypertonic glucose The latter, as Dr Zintel has indicated, is particularly important Glucose fills not only temporary osmotic needs, but, as a metabolizable foodstuff, also to an extent replaces 'caloric" deficiency Details of the latter phe nomenon are out of place here, but carbohydrates act as protein, fat, water and salt (Na^+ and K^+) sparers Glucose has a multi barreled attack, through its manifold interrelationships in the highly integrated metabolic activity Without further discussion, it may be obvious that each of these ' sparing effects of glucose, on protein, on fat and on water and salts, is of pertinence in the present problem

As soon as the blood circulation has been improved, and, thereby, a good degree of kidney function restored (as evident from a drop towards normal in the plasma protein concentration and in the N P N , and in the production of an adequate flow of urine), we are prepared for the *second stage* of replace ment therapy The first stage is in the main an emergency measure Do first things first The body s acid-base and water balance is so dependent on the kidneys that the situation is quite hopeless until renal disability has been corrected The second stage, a more leisurely one, is designed to meet more adequately the needs for replacement of the body s deficits It is in this stage that I would place desirable, but less important things, like procedures for the reestablishment of the normal acid-base pattern, through the judicious use of acidifying solutions, as NH_4Cl *It is only in this stage, when adequate renal function has been insured, and if direct proof of potassium deficiency is at hand, that therapy may be directed to provide this specific need* This will be further discussed Dr Bockus perhaps has in mind a case in which severe renal insufficiency exists, and in which restoration of some degree of function is difficult Such cases present exceptionally hard problems, and the bio- chemist, like the clinician, is hard put to it

We may now turn to the first question, which has to do with the quanti tative aspects of replacement therapy and the character (composition) of the solutions used This is not easy to answer, since the situation varies with the case, the size and age of the individual, the past history (speed of develop- ment), the renal performance, and the plasma chemistry, which, as has been discussed, only serves for an approximation of the extent of the body s deficits The situation may also be modified by the factor of allowable time, as in the patient being prepared as well as possible, but as rapidly as possible, for rather serious surgery In the latter case, perhaps only the *first stage* of therapy can be carried out, with the *second stage* started before operation and completed postoperatively, when other factors may have to be considered

In general terms, in our particular adult subject, it has been suggested that intravenous therapy was started with about 1 liter of isotonic saline and 1 liter of glucose solution This first measure was designed to correct for the hypovolemia and to afford conditions conducive to relief from renal functional impairment Having accomplished the latter, we have brought to our aid the body s natural means for combating acid base and osmotic imbalance However in the acute case, attended by large body deficits, further aid is usually necessary for osmotic factor replacement and for a more rapid adjustment (than can be accomplished by the unaided kidneys) of the normal acid-base pattern In this phase of replacement therapy, the quantitative needs cannot be estimated with exactness In our subject the total body deficit of osmotic factors was estimated as six times or more, perhaps ten times, that of the total plasma deficit In terms of 0 9 per cent NaCl solution this would correspond to between 3 and 5 liters Of course this does not mean that we restrict replacement to NaCl nor that we proceed without caution, to inject large volumes even though slowly It is now time to do something about the alkalosis and a fraction of the total fluid therapy may be in the form of an acidifying solution NH_4Cl

It has been said that nothing under the sun is wholly inert physiologically Thus, we have such phrases as 'water intoxication and oxygen toxicity Therapy with bland NaCl may be overdone, but the parenteral administration of acidifying or alkalinizing solutions as the case demands, is a quite different proposition from the use of relatively harmless neutral NaCl or glucose in moderate amounts The moment such acidification or alkalinization therapy is introduced, it becomes imperative to avoid over therapy with at times bad consequences This can only be done by guidance afforded through frequent periodic analyses of the blood, and perhaps also the urine The latter has unfortunately of late been neglected In many of these cases it is not sufficient to be guided by the plasma bicarbonate (CO_2 content) alone An example may suffice It is now recognized (Singer and Hastings) that in the alkalinization therapy of diabetic acidosis, the plasma pH may change from let us say 7 0 to 7 6 when the CO content is still appreciably below normal What has happened is that overventilation has continued when there was no longer any need for blowing off excess CO Result *metabolic acidosis* has been replaced by *respiratory alkalosis* There have been many cases in the past of over therapy in this state when the administration of the alkaline replacement solution was guided solely by the inadequate light of the return of CO_2 content towards normal Thus, besides the alkaline reserve one should also determine under these conditions the pH of the plasma

It is desirable to mention the pH of the urine as a useful guide By means of suitable color standards it is easy to quite accurately estimate the urinary pH Its value, in guiding replacement therapy may be illustrated also by the case of diabetic acidosis Before treatment the urinary pH was about 4 8, about as acid as the urine can get The kidneys are here functioning to their utmost capacity to excrete metabolic acids from the body Alkalinization

therapy may be stopped, or, at least, further alkali should not be administered, except with great caution, if the pH of the urine shifts only 0 2 to 0 3 of a pH unit, from 4 8 to 5 0 or 5 1 This slight shift is the warning signal. It indicates that the kidneys no longer are forced to operate at their physiologic maximum for the excretion of acid There is no longer real need for aid from the outside Trouble and responsibilities increase manifold as replacement therapy begins to involve solutions a little more complicated than those of isotonic saline or glucose

Potassium One would fly headlong against the dictates of today s fashion, if one were to omit potassium from a discussion of replacement therapy I do not wish to be exceptional, and, therefore, I shall make a few comments on this phase of the subject Let us return to the particular patient with acute pyloric obstruction, whose blood chemistry was presented in detail Replacement fluid therapy with NaCl, glucose, and NH_4Cl solutions was effective in *reversing his dehydration state and restoring his acid-base balance near* enough to normal to permit successful surgery He recovered fully, and without benefit of potassium administration Lest this remark be construed as a Pollyannaish satisfaction with the state of things as they are, I hasten to add that some related questions remain unsettled although with reference to *this particular individual they will probably never be answered If he had* been given potassium replacement therapy, would he have recovered faster, or, would his chances for survival and recovery have been greater, or, would his case have worried the attending physician and surgeon less? This is a difficult question It has been answered in the case of Addison s disease and periodic paralysis *However I believe I am correct in saying that it cannot* be answered at present for cases of acute pyloric obstruction, nor am I certain whether an affirmative answer can be supplied with assurance in certain other conditions It is, however, a particularly cogent question which proponents of potassium replacement therapy should be prepared to answer in proposing this form of specific medication

Now what do we know concerning the state of potassium in our subject with acute pyloric obstruction?

(1) As we have mentioned before therapy he happened to have actually a slight hyperkaliemia or hyperpotassemia

(2) He was dehydrated and was oliguric—had renal disability We must again emphasize this point, since it is crucial in the present connection

(3) After the first stage of therapy with restoration of his plasma volume towards normal and with relief from his relative anuria analysis showed that the plasma K^+ was now somewhat below normal—slight hypokaliemia It is this sign *from which we infer the probable existence in this subject* of some degree of body potassium deficit, potassium cytopenia, incident to the loss of intracellular fluid This *inference* can be made with a fair degree of certainty, since intracellular fluid, *in equilibrium with* extracellular fluid, must have been lost with the latter in the development of this individual s state But inference *it remains*, since our present knowledge of intracellular fluid is, at best, fragmentary, and direct information as to tissue compositions in

such cases is usually not available Perhaps information of this sort should be sought, at least under controlled experimental conditions

Should potassium have been administered to this patient?

(1) After renal function had been restored and after the satisfactory demonstration of the hypokaliemia potassium could have been given, and possibly with benefit Objectively, at this stage, we can go no farther in our appraisal of this particular case

(2) We can, however, be very definite in one important regard During the first stage of therapy, before adequate renal function had been established, the *administration of potassium was contraindicated* This may seem obvious owing to the fact of hyperkaliemia But it should be stressed that this finding is not invariable Even in the absence of an elevated level of K^+ in the plasma, this ion must not be administered to subjects with renal disability This is not the only but it does appear to be the main contraindication to potassium replacement therapy I do not know what would have happened to our subject if he had been inadvisably given potassium during the primary therapeutic phase, but the chances are it would not have been good This serious warning is not the result of personal prejudice, but has been explicitly given by leading proponents of potassium therapy (Darrow, Elkinton)

The replacement of K^+ differs in certain respects from that of Na^+

(1) The conduction apparatus of the heart is particularly sensitive to (as illustrated in Dr Bellet s work), and may be adversely affected by an eleva tion above normal in the plasma K^+

(2) In contrast with Na^+ replacement, in which one puts Na^+ more or less directly where it is needed in the extracellular fluid (plasma and inter stitial fluid), K^+ medication is designed to correct for a deficit largely in the intracellular compartment Thus potassium replacement solutions some with concentrations of K^+ six to tenfold greater than in normal blood plasma (so as to imitate more closely the composition of intracellular fluid), are frequently administered In parenteral medication the K^+ ion reaches its cellular destination indirectly via the blood stream This is one reason why effective circulation and adequate kidney function are required since other wise the blood would be overwhelmed by the unusual influx of potassium

For an appreciation of some of the complications in fluid and ionic balance the equilibrium which exists between intra- and extracellular fluid must be kept in mind Cellular and vascular membranes possess special properties and the movement of materials across them is not the simple matter of diffusion through permeable membranes This is obvious from the fact that at equilibrium intracellular fluid is high in K^+ low in Na^+ while extra-cellular fluid is strikingly opposite in this regard Permeability to ions is now recognized to be relative Metabolism within the cells has an influence upon this property as probably does hormonal control (adrenal cortex factors, etc) Hormonal control is particularly concerned with the renal adjustment (through differential excretion) of the normal plasma level of Na^+/K^+ Thus, in the absence of functional derangement the plasma (and probably the cellular) ratio of Na^+/K^+ remains essentially unchanged, even with an oral

intake of as much as 20 gm of KCl The primary and main fluid loss in acute pyloric obstruction is that of an extracellular fluid, gastric juice, high in Na^+ and H^+, low in K^+ The loss of intracellular fluid may be looked upon as secondary, incident both to reequilibration with a depleted extracellular fluid, and to an attending tissue breakdown The situation is clearly not a simple one There does not exist, and it would be improper to imagine, a simple sequence of events, such as a pitcherful of extracellular fluid, low in potassium, poured out, and a pitcherful of intracellular fluid, high in potassium, poured in to take its *place If this sort of thing were to occur*, we might expect in dehydration states to find invariably (which we do not) a hyperpotassemia accompanying the potassium cytopenia The deduction which one may draw from these remarks is that the process of restoration of intracellular fluid, under the influence of potassium administration, involves similarly complicated factors of adjustment One just doesn t pour a pitcher ful of ersatz intracellular fluid in When resort is made to such medication, the need for it should be fully established The attending physician must recognize that added responsibilities have been assumed, that the progress of therapy must be rigidly followed, if undesirable consequences are to be avoided

Dr Bockus Dr Drabkin, this question is asked What preparation of potassium do you recommend? Where can it be obtained? How much do you give? What are the precise indications for its use? Dangers of using potassium? Describe method of determination of serum potassium

Dr Drabkin I am afraid that I must skirt one of these questions, Dr Bockus ' What preparation of potassium do you use, and where can it be obtained? We laboratory men are at a disadvantage When we need solu tions, we usually make them from reagents on the shelf This practice has one obviously bad feature about it—the laboratory worker can t blame the dispenser of the prepared solution for the results Again, in general, some clinicians have employed 0 2 per cent KCl, mixed with glucose I see no reason why KCl cannot be employed together with an acidifying solution like NH_4Cl *As already mentioned, potassium containing* alkalinizing solu tions, when these are required, have been employed One such isotonic repair solution is Darrow s, with a fairly high concentration of potassium lactate, in appropriate mixture with NaCl The quantities to use? Estimate, judge, watch and hope

Question two has to do with the determination of plasma or serum potas sium The modern determination of potassium is by *means of the flame photometer* This instrument is responsible for reviving clinical interest in potassium, and gives promise of greatly extending our knowledge of potassium metabolism, with its enlarging implications Chemical determinations of plasma potassium were not of the greatest desirable accuracy, and the an alytical procedure was onerous Hence, the clinical chemist was tempted to avoid this subject Flame photometry, on the other hand, *appears* compara tively "easy " That is the present difficulty It just appears easy As one personally much interested in photometry, I think I may be permitted to

state that one can make as large errors (if not larger errors) with a special apparatus costing $1500 to $2000 as with the acknowledgedly difficult chemical method In the latter case one has learned to use care With the new method, I am afraid that carelessness may be engendered I am all for flame photometry It is a fine technic, but it requires rigid control and besides specialized skill in the technician responsible for its use No method has as yet been devised which is foolproof, in which the turn of a crank furnishes the right answer

I have reserved for the last that part of Dr Bockus question in which the words dangers of potassium were used I believe that I have already answered this question or, at least, have indicated what I regard as a judicious position I wish to make several points clear, so that no misinterpretation may result

(1) These comments have to do with the over-all subject of potassium re placement, and are not directed towards the interesting studies of potassium which have been reported here

(2) Potassium replacement therapy is an important development It is here to stay

(3) It is not fair to say unreservedly Potassium is dangerous I have no doubt whatever that there are appropriate disease states in which relatively large amounts of potassium salts may be administered with impunity, and with benefit as discussed by Dr Bellet

(4) However, K^+ is a physiologically different sort of ion than Na^+ K^+ can neither be taken nor administered lightly One of the different things about potassium and fortunate things, is that you can t inject its salts too fast I say can t advisedly The patient if he is not comatose, won t let you He gets vascular spasm and it hurts Potassium replacement therapy must be rigidly controlled its progress followed by frequent analyses of plasma K^+ Dr Bellet does a fine job He carefully follows therapeutic progress by means of a continuous electrocardiographic record Has he thought it necessary to do this when isotonic saline or glucose were administered? I think he recognizes that potassium medication belongs to a somewhat dif ferent class How many of you are prepared to follow therapy as Dr Bellet has done?

(5) Finally potassium medication can be dangerous if given to patients with certain types of heart disease and especially, if administered to sub jects with renal disability or impairment, so frequently encountered in dehy dration states I have already sufficiently emphasized this point and I am sure Dr Bellet must agree that under such conditions potassium is defi nitely contraindicated

I have been impressed with the case which has been made out for the need of potassium replacement in diabetic acidosis coma and post-coma (as presented by Dr Bellet and his colleagues as well as others) I have been a great deal less convinced by the present proof of a similar need in acute obstructive disease of the intestine Dehydration is present in both states otherwise they are far apart The common feature does contribute certain

similarities The untreated case of both pyloric obstruction and diabetic coma may exhibit the 'paradox' of hyperpotassemia and potassium cytopenia In each, kidney shutdown may be present If so, in the first stages of the therapy of each, potassium medication is contraindicated Later, in diabetic acidosis, in what may be called the post-coma phase of treatment, potassium administration may be of real value It is often possible, at this stage, to give the potassium orally However, this does not mean that one can now afford to omit objective checks upon the patient s blood potassium, and/or his electrocardiogram It is possible that potassium depletion (cytopenia) may be of a more severe grade in diabetic coma than in acute pyloric obstruction, but we have no real information on this point In the diabetic, however, the case has been clarified in one way, orally administered potassium is avidly retained by the body—presumptive evidence of deficiency and need (Danowski et al) As Dr Bellet has mentioned, K^+ may have a special role in sugar metabolism It may possess some function in regard to glycogenesis The point is unsettled and *it is unimportant to argue it It appears* that the degree of potassium deficit which develops in these cases is beyond that which can be explained solely by potassium "liberation' through glycogen breakdown and also by tissue protein destruction It is likely that *long before coma intervened, important body deficits had already developed* During this much longer developmental stage (in contrast with acute pyloric obstruction), large volumes of urine, containing sugar, protein wastes and K^+, were leaving the body

Potassium replacement therapy (recognized for some time by pediatricians) is, nevertheless, a relatively new tool Its full potentialities and its exact position in the therapeutic armamentarium remain to be disclosed During this period of assessment, the pathway of wisdom, which will insure and not hinder progress *in this important field, would seem to be to temper enthu*siasm with caution, a caution particularly appropriate to a substance so biologically potent as the potassium ion

Dr Bockus *A question for Dr Bellet In intestinal obstruction one can* have a decrease in the calcium ion, does not that produce changes in the electrocardiographic picture?

Dr. Bellet Decrease in the calcium ion does produce changes in the electrocardiogram, *but the changes due to depletion in the calcium ion are* of a different order, and we can differentiate them in the electrocardiogram We ve had some instances as yet unpublished, where we have observed the combination of hypopotassemia and hypocalcemia, and it is of interest that when we correct *for the calcium ion there is observed an immediate* electrocardiographic effect within about a minute or two after 10 to 20 cc of 10 per cent calcium gluconate has been administered intravenously If we correct for one ion we will not correct for the other, if we supply both there results a complete *restoration of the electrocardiogram to normal*

Question Dr Tumen, could you very briefly comment on the treatment of intestinal obstruction in a cardiac patient who was previously, but not now in failure?

Dr Tumen That s a rather difficult question The specific case of course, would present a great many individual problems I think that one would have to be guided entirely by whether or not the obstruction was complicated by we ll say, strangulation, whether there was an immediate operation in the offing, how much shock the patient was in, etc If we happened to be faced with an obstruction in which there was no immediate cause for surgery, in which the question of strangulation wasn t introduced, in which the patient did not have a type of closed loop obstruction or acute colonic ob struction with extreme over distention, then, of course there would be ample time to decompress the patient and use rapid digitalization with digitoxin or one of the other rapid methods I should think under those circumstances that the relief of the abdominal distention with the Miller Abbott tube would probably contribute greatly to the relief of cardiac em barrassment If on the other hand, one were faced with the necessity for immediate operation i e , strangulation obstruction I think the thing to do probably then would be to digitalize as rapidly as possible and perform the operation and try to worry along with the problem later

Question Doesn t plasma have a very significant amount of sodium chloride? Why is sodium chloride not harmful in this form as well as in the form of physiologic salt solution?

Dr Zintel Plasma does contain sodium chloride of course I think we could probably use Dr Drabkin s pitcher example here With a reduced blood volume one pitcher of transfused plasma is added to five pitchers of plasma which is already in the vascular system The pitcher of transfused plasma which is added remains in the vascular system for a considerable time Since the sodium chloride concentration of the infused plasma and the plasma already in the vascular tree are equal or nearly equal there will be no ill effects from the sodium chloride of the transfused plasma

✓*Question* Will not the administration of 5 per cent glucose intravenously produce dilution of electrolyte and plasma proteins and be harmful by producing lower concentrations?

Dr Zintel A 5 per cent glucose solution is not retained for very long periods of time in the vascular tree, it is rapidly passed on and excreted Although there is a very slight dilution factor this dilution could not be significant unless very large quantities were used in a very short period of time Nine to 10 liters of water are required to produce water intoxication in a period of twenty four hours The glucose ordinarily is almost completely utilized and as such is a source of caloric intake to the body

I would like if I may, to emphasize that one ought not to attempt to

similarities The untreated case of both pyloric obstruction and diabetic coma may exhibit the paradox of hyperpotassemia and potassium cytopenia In each, kidney shutdown may be present If so, in the first stages of the therapy of each, potassium medication is contraindicated Later, in diabetic acidosis, in what may be called the post-coma phase of treatment, potassium administration may be of real value It is often possible, at this stage, to give the potassium orally However, this does not mean that one can now afford to omit objective checks upon the patient's blood potassium, and/or his electrocardiogram It is possible that potassium depletion (cytopenia) may be of a more severe grade in diabetic coma than in acute pyloric obstruction, but we have no real information on this point In the diabetic, however, the case has been clarified in one way, orally administered potassium is avidly retained by the body—presumptive evidence of deficiency and need (Danowski et al) As Dr Bellet has mentioned, K^+ may have a special role in sugar metabolism It may possess some function in regard to glycogenesis The point is unsettled and it is unimportant to argue it It appears that the degree of potassium deficit which develops in these cases is beyond that which can be explained solely by potassium liberation' through glycogen breakdown and also by tissue protein destruction It is likely that long before coma intervened, important body deficits had already developed During this much longer developmental stage (in contrast with acute pyloric obstruction), large volumes of urine, containing sugar, protein wastes and K^+, were leaving the body

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I would like, if I may to emphasize that one ought not to attempt to

overcome dehydration and hypochloremia and at the same time neglect an associated hypoproteinemia All of these factors go hand in hand If you give excessive amounts of sodium chloride solution to the hypoproteinemic patient, edema, which may cause serious physiologic disturbances in the surgical patient, will be produced

DR BOCKUS Isn t that the real reason why you have become a little fearful of the use of chloride, Dr Zintel?

DR ZINTEL Since we have discontinued the practice of administering the equivalent of 1 liter of saline solution (8 5 gm NaCl) as part of the patient s daily fluid intake, there has been a change in the clinical condition observed in the patients When sodium chloride solutions were used routinely during the operative and immediate postoperative periods, an occasional patient had puffiness of the face and neck, lethargy and urine of small volume On the second or third postoperative day, a marked diuresis would occur, the edema would disappear and subjectively and objectively the patient would be greatly improved This phenomenon, I am sure, represented the postoperative fluid and electrolyte retention described by Coller At the present time sodium chloride solutions are administered only when there is a need for sodium chloride as indicated by the serum chloride level

Current Problems of Diagnosis and Therapy

THE MODE OF ACTION OF DRUGS UPON THE AUTONOMIC NERVOUS SYSTEM*

JULIUS H COMROE, JR , M D

This paper will deal with drugs which act upon the peripheral parts of the autonomic nervous system As its title implies, its purpose is to classify these drugs according to their site and mode of action, rather than to describe their clinical use in any detail, for this latter purpose the reader must refer to other literature

The drugs under discussion do not act upon the preganglionic fibers postganglionic fibers, or upon nerve endings per se, but have their characteristic effect at points where the nerve impulse is transmitted from pre ganglionic fiber to the ganglion cell or from the postganglionic fiber to the tissue receptor substance (Fig 235) Since it is reasonable to believe that their mode of action is intimately concerned with the transmission of the nerve impulse it is important to discuss briefly one widely accepted concept of this transmission—the humoral concept This concept was developed by Otto Loewi and Sir Henry Dale who were awarded the 1938 Nobel Prize in Medicine and Physiology in consequence Loewi showed that when a nerve impulse arrives at a parasympathetic nerve ending, a chemical substance is released which in turn produces the final action upon the organ innervated He first demonstrated this in the following classic experiment A frog s heart was perfused with a fluid which was then collected and used to perfuse a second frog s heart When the vagus nerve to the first heart was stimulated, this heart slowed in characteristic fashion A few moments later the second heart, completely unconnected with the first except for the fact that it received the perfusate which had passed through the first heart, also slowed The conclusion was inescapable that vagus stimulation had resulted in the liberation of a chemical substance (vagustoffe) which diffused into the perfusion fluid was carried to the second heart and there reproduced all of the effects of vagus stimulation which had occurred in the first heart It was soon discovered that this chemical substance possessed all the chemical and biological characteristics of acetylcholine Loewi and other investigators then demonstrated that this observation was not only true in the case of the vagus but that acetylcholine was also liberated by postganglionic nerve impulses throughout mo t of the parasympathetic, or craniosacral division of the autonomic nervous system Similar investigations carried out upon the sym

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pathetic nervous system showed that stimulation of the postganglionic fibers of this division led to the liberation of a chemical substance, 'sympathin,' quite different from acetylcholine, but almost identical with epinephrine or adrenaline Thus it has been fairly well established that the postganglionic impulses are transmitted to the effector organ, at least in part, by the libera tion of a chemical substance characteristic for each division of the autonomic nervous system

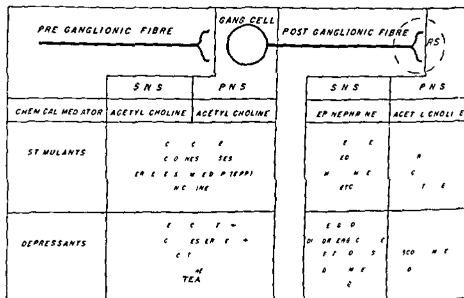


Fig 235 Diagrammatic outline of the mode of action of drugs upon the autonomic nervous system

SNS = Sympathetic Nervous System
PNS = Parasympathetic Nervous System
RS = Receptor Substance

Note that all the drugs listed act either upon the ganglion cell or upon the receptor substance The anticholinesterase drugs actually have no direct effect upon either of these structures and are listed because they prolong and intensify the action of acetyl choline at these sites + + indicates that large doses of the drug are needed to produce that particular effect

When the transmission of nerve impulses through ganglia was investigated with this humoral concept in mind, it was found, in the *parasympathetic* nervous system, to be associated again with the liberation of acetylcholine at the terminations of the preganglionic fibers Transmission from the pre ganglionic fiber to the ganglion cell in the *sympathetic* nervous system is also accompanied by the liberation of acetylcholine (rather than the liberation of epinephrine as might have been anticipated) This finding of chemical identity between the two divisions of the autonomic system is of tremendous importance in understanding the actions of drugs upon ganglionic trans mission for it would lead one to expect that the drugs acting upon the

ganglion cells of the parasympathetic nervous system would have similar actions upon those of the sympathetic nervous system

DRUGS WHICH AFFECT SYMPATHETIC GANGLION CELLS

STIMULANTS

Acetylcholine As would be expected from the humoral theory of nerve transmission, acetylcholine has the property of stimulating ganglion cells of the sympathetic nervous system This action is of little practical value since stimulation occurs only with relatively large dosage and since the effects of acetylcholine are extremely transient in the human body

Nicotine Low concentrations of nicotine stimulate sympathetic ganglion cells It is possible that some of the so called direct effects of nicotine upon the heart may be attributed to this action upon the sympathetic ganglion cells which innervate it

DEPRESSANTS

Acetylcholine In still higher concentrations than those which stimulate sympathetic ganglia, acetylcholine can depress and block ganglionic trans mission

Nicotine As in the case of acetylcholine this drug has a depressant effect in higher concentrations This action is of little clinical usefulness because of the widespread side-effects of nicotine upon other cells such as those of the carotid and aortic bodies the skeletal muscle motor end plates, and the neurones in the central nervous system

Curare and Curare like Drugs These drugs have a highly specific effect in low concentration upon neuroskeletal muscular transmission but in very large dosage can also block sympathetic ganglia This effect is clinically unimportant since it occurs only with concentrations of curare that are nearly lethal

Tetraethylammonium (TEA, Etamon) In therapeutic concentrations this drug can block transmission from the preganglionic fibers to the ganglion cells in both the sympathetic and parasympathetic nervous systems [5] Its action is best described as a decentralization of the whole autonomic nervous system since the administration of TEA does not prevent the response to sympathomimetic and parasympathomimetic drugs which act more peripher ally than the ganglia The symptoms produced by TEA are not paralysis of the innervated organs as one might expect but rather those which follow block of that division of the autonomic nervous system which possesses the highest tonus for the organ in question For example in the case of the eye administration of TEA leads to a slight mydriasis, because the parasympathetic oculomotor nerve possesses greater resting tonus than the sympa thetic innervation Similarly, acceleration of the pulse occurs because of the blocking effect upon the cardiac vagus Dryness of the mouth decreased sweating decreased motility of the gut and bladder, dilatation of the peripheral and nasal vessels and in somewhat larger dosage, muscular weakness

pathetic nervous system showed that stimulation of the postganglionic fibers of this division led to the liberation of a chemical substance, 'sympathin,' quite different from acetylcholine, but almost identical with epinephrine or adrenaline Thus it has been fairly well established that the postganglionic impulses are transmitted to the effector organ, at least in part, by the liberation of a chemical substance characteristic for each division of the autonomic nervous system

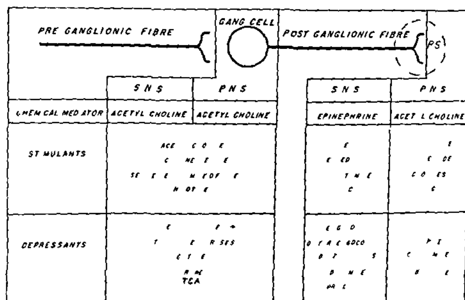


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(2) By the simultaneous use of ephedrine or cocaine, each of which augments and prolongs the activity of epinephrine

(3) By the use of peripheral blocking agents which reduce or abolish its activity (See below)

It must be emphasized again that epinephrine and all of the epinephrine derivatives and substitutes (such as ephedrine, amphetamine and methedrine[10]) act at the most peripheral portion of the sympathetic nervous system They continue therefore, to be fully effective even though the sympathetic nervous system is blocked by spinal anesthesia or by ganglionic blocking agents

DEPRESSANTS (TABLE 36)

These blocking agents do not actually prevent the liberation of epinephrine by postganglionic nerve impulses but they reduce its effectiveness whether it be liberated or injected They accomplish this by a preferential occupation of the cell receptors, thus interfering with the chemical combination between epinephrine and the tissue They may be both adrenolytic (blocking the action of circulating epinephrine) and sympatholytic (blocking the effects of stimulation of the sympathetic nervous system)

The drugs which fall into this group are ergotoxin (too toxic for effective clinical use), dihydroergocornine,[1] dibenamine[15] priscol[4, 9, 8] and the benzodioxanes (F933 833)[8] They have been used in a variety of ways in clinical medicine

(1) As a diagnostic test for pheochromocytoma they are useful because their adrenolytic effect appears with lower concentrations than does their sympatholytic effect in other words, they can block the effect of epinephrine liberated into the circulation by the adrenal medulla before they block the normal sympathetic nerve impulses Hypertension due to excessive circulating epinephrine is therefore lowered by a dosage which is too small to block the normal sympathetic nerve impulses which are partly responsible for maintaining normal blood pressure

(2) In treating the effects of epinephrine overdosage their rationale is obvious

(3) They have also been used to diagnose the existence and degree of sympathetic vasoconstriction in patients with peripheral vascular disease or with hypertension It must be remembered that these drugs have a tendency to block vasoconstrictor fibers throughout the body and, on this account a precise prophecy of the effects of surgical extirpation of localized portions of the sympathetic nervous system cannot be based upon their use Furthermore, their prolonged use in the treatment of chronic vasospasm is probably inadvisable since they may block so many parts of the sympathetic nervous system that they reduce its value to the body in times of emergency Difficulties might then be expected in the form of postural hypotension or of severe hypotension from a moderate degree of hemorrhage

also occur It has been reported that these effects of TEA may be antagonized by neostigmine [11]

TEA has been used clinically as a preliminary test to predict the effectiveness *of sympathectomy in patients with hypertension* or peripheral vascular disease, and for the treatment of hypertension, peripheral vascular disease and peptic ulcer TEA has considerable usefulness in the emergency treatment of bed patients suffering from vasospasm, pulmonary embolism, spasm of the gastrointestinal tract, and causalgia Deaths have occurred following the use of TEA in hypertensive patients, presumably as a result of coronary insufficiency due to a sharp fall in blood pressure

It is open to objection as a preliminary diagnostic test because it blocks the whole autonomic nervous system and not merely the segments of the sympathetics that it is proposed to remove surgically It is open to objection as a therapeutic *tool because it produces postural hypotension and inability to* compensate normally for hypertension and hypotension, it may also be responsible for difficulty in urination and defecation

DRUGS WHICH AFFECT THE SYMPATHETIC POSTGANGLIONIC RECEPTOR SUBSTANCE

STIMULANTS

Epinephrine Since epinephrine is liberated by nerve impulses arriving at postganglionic terminations, it is reasonable that its injection should mimic all of the effects of postganglionic stimulation of sympathetic nerves This it does and for this reason is termed a sympathomimetic drug The clinical usefulness of sympathomimetic drugs depends upon their property of augmenting the rate and force of cardiac contraction, of constricting certain vessels, *of raising or maintaining blood pressure, of dilating the bronchioles,* of relaxing smooth muscle in the gut and urinary bladder, and of stimulating the central nervous system

The action of epinephrine may be modified in a number of ways

(1) By section of the postganglionic fibers This leads to a marked increase in sensitivity to the action of epinephrine The phenomenon is of considerable practical importance in considering the type of sympathectomy to be performed in *the treatment of peripheral vascular disease Preganglionic* section preserves the integrity of the ganglion cells and postganglionic fibers, so that degeneration does not occur and sensitization to epinephrine does not result However, if a *post*ganglionic section is performed marked vasospasm may result whenever epinephrine appears in the circulation, whether by liberation from the adrenal medulla or from therapeutic injection When sympathectomy is extensive enough to include denervation of the adrenal medulla, the reflexes which ordinarily *lead to epinephrine secretion become ineffectual,* under these circumstances, therefore, the problem of sensitization to epinephrine loses its importance unless the drug be injected, or unless substances which stimulate directly the ganglion cells of the adrenal medulla are administered

DRUGS WHICH AFFECT PARASYMPATHETIC GANGLION CELLS

STIMULANTS

As one would expect on the basis of the cholinergic concept, these drugs are the same as those which stimulate sympathetic ganglion cells

DEPRESSANTS

These, again are the same drugs which depress sympathetic ganglion cells The only clinically important member of the group is tetraethylammonium (TEA)[5] Though this drug has been discussed under depressants of sympathetic ganglia, its effect is certainly not limited to this objective, since it can, and in appropriate dosage does block ganglion cells in both the sympathetic and parasympathetic nervous systems

DRUGS WHICH AFFECT THE PARASYMPATHETIC POSTGANGLIONIC RECEPTOR SUBSTANCE

STIMULANTS

Pilocarpine and Furmethide (Furfuryl Trimethylammonium Iodide)[3] These drugs are used clinically chiefly for their local action upon the eye

Cholines Acetyl betamethylcholine (methacholine) carbaminoylcholine (doryl, carcholin, carbachol) and carbaminoyl betamethylcholine (urecholine) also act upon the receptor substance in the tissues Consequently they can produce their characteristic effects even after such surgical procedures as vagotomy They may be used to contract smooth muscle in the gut[13] urinary bladder or eye (in the last by local instillation) to increase sweating, salivary and pancreatic secretions, and to stimulate the cardiac vagus in order to abolish certain types of tachycardias

Anti-cholinesterase Substances When acetylcholine is liberated by postganglionic parasympathetic nerve impulses it is very quickly destroyed by a special enzyme called cholinesterase A number of substances have the specific property of inactivating cholinesterase either temporarily or permanently Temporary inactivation is produced by eserine (physostigmine), neo stigmine (prostigmin) and TEPP (tetraethyl pyrophosphate)[17] DFP (diisopropyl fluorophosphate) in sufficient dosage, can permanently inactivate it and therefore produces effects which last for days or weeks until the enzyme is regenerated by the body *[6] These drugs have the property of prolonging and intensifying the normal actions of acetylcholine wherever it may be produced in the body Thus they can produce postganglionic parasympathetic stimulation or ganglionic stimulation in the parasympathetic and sympathetic nervous system (including in the latter instance, the adrenal medulla) For reasons which are not clearly understood when these drugs are given sys

* Neostigmine and DFP probably act upon the same cellular mechanism for if DFP is administered at the height of neostigmine action permanent inactivation of cholinesterase (and long lasting effects) will not result. This is explained by postulat ing that DFP cannot combine with receptors already occupied by neostigmine and that DFP is itself destroyed in the body before the neostigmine is eliminated

Table 36

DRUG	DOSAGE	ROUTE	LENGTH OF ACTION	SIDE EFFECTS
Dibenamine	*5 mg/kg*	I V	36–96 hrs	Local tissue necrosis and phlebothrombosis *miosis*, nasal congestion, confusion emotional lability restlessness, nausea and vomiting
Dihydroergocornine (DHO 180)	0 1–1 25 *mg*	I V	2–3 hrs	Nasal *congestion, postural hypotension, fatigue* headache nausea and vomiting tachycardia thirst irregular respiration
Priscol	25–75 mg 25–50 mg /3–4 hrs	I V or I M Orally	3–8 hrs	Sensations of warmth crawling in skin hair rising chilliness and apprehension and tachycardia nausea postural hypotension nasal congestion headache
Benzodioxane	10–20 mg	I V	15 min	Tachycardia, flushing, palpitation, nervousness dizziness headache *hyperpnea*, cold extremities

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DIFFERENTIAL DIAGNOSIS OF JAUNDICE

HENRY J TUMEN, M D

The subject of the differential diagnosis of jaundice is a topic of perennial discussion The reason for this is obvious During the past twenty years there have been tremendous advances in our knowledge of hepatic disease and in what we might call the applied physiology of the liver We can now speak with a great deal of statistical accuracy about hepatic disturbances and about jaundice Nevertheless, every physician knows that he sees patients with jaundice in whom the problem of the recognition of the cause of the jaundice still presents a great deal of difficulty Our knowledge of jaundice as a major problem has increased but our knowledge as applied to the individual patient still has a great many defects It is for that reason that discussions on the differential diagnosis of icterus are still on programs and still offer food for thought

METABOLISM OF BILIRUBIN

I should like to begin this discussion by speaking very briefly about the metabolism of bilirubin recalling the various steps in its formation and excretion emphasizing the fact that it is formed by the breakdown and disintegration of hemoglobin from dying red cells and that it is excreted by the liver cells into the bile canaliculi In the process of its excretion it is converted from the so-called indirect reacting bilirubin or bilirubin globin to the direct reacting bilirubin It finally passes into the bile channels and reaches the intestinal tract there being converted to urobilinogen and is finally excreted from the body in that form There may be disturbances of any of these steps which lead to the accumulation in the blood stream of bilirubin and the development of clinical jaundice There may be an excessive destruction of red cells as a result of various hemolytic processes beyond the normal capacity of the liver cells to excrete bilirubin There may be either destruction or dysfunction of the liver cells, so that they lose their ability to excrete the

temically they seem to have more effect upon the gastrointestinal tract and bladder, *and possibly upon the bronchioles, than they do* upon other organs innervated by the autonomic nervous system In consequence they are useful for counteracting atony of the gastrointestinal tract[9] and bladder, but must be sedulously avoided in patients with bronchial asthma

They also have an action upon skeletal muscle, which is compatible with the interesting hypothesis that neuromuscular *transmission is mediated* by the liberation of acetylcholine at the motor end plates Because of this action, neostigmine is very valuable in the symptomatic treatment of myasthenia gravis DFP, when used for the same purpose, has a longer lasting but less powerful effect and is more apt to produce undesirable side effects on the gastrointestinal tract and central nervous system [6]

This group of drugs may be used locally in high concentration in the eye as miotic and cycloplegic agents The effect of eserine and neostigmine, used for this purpose, lasts about two to three hours whereas that of DFP persists for days to weeks The resulting miosis and decrease in intra-ocular pressure are of considerable value in the treatment of glaucoma [1, 14]

DEPRESSANTS

These drugs do not prevent the liberation of acetylcholine but probably combine specifically with the receptor substance upon which acetylcholine would normally act Interestingly enough one choline derivative (dibutoline[16]) exerts a blocking effect of this sort However, atropine and other belladonna derivatives are the drugs most commonly used for this purpose Their actions are too well known to merit discussion in this place but two of their characteristics should be mentioned (1) They do not prevent the action of acetylcholine everywhere that it is liberated in the body, but only at the postganglionic parasympathetic receptor Thus they do not block ganglionic transmission or neuromuscular transmission (2) Though atropine has a highly specific action at the postganglionic receptors, it blocks them with varying degrees of ease Certain parts of the parasympathetic are blocked by concentrations which appear to have no effect on other organs Thus, secretions of the eye, nose and throat are blocked by small doses, paralysis of the ciliary muscle, *the circular muscle of the iris, and the cardiac vagus* requires increasingly large doses, and complete block of the gastrointestinal branches of the vagus requires very large doses

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regurgitation in character In other words in the early stage of liver damage, according to Rich, hepatocellular jaundice is the result of bilirubin retention, and in the later stages it is considered to be the result of regurgitation Another major difficulty from a clinical standpoint is the fact that under regurgitation jaundice are included those two forms of jaundice which the clinician has to differentiate most often the jaundice that is a result of necrosis or damage to the liver cells and the jaundice that is due to biliary obstruction Since our major problem in differentiation as I will mention in a moment is a differentiation of those two it seems a little weak to include them both in the same general category

CLASSIFICATION OF JAUNDICE

(Adapted from McNee)

Hemolytic
Hepatocellular
Obstructive

Another classification is the one that was introduced originally by McNee This is extremely simple, and divides jaundice into three major forms—hemolytic, hepatocellular and obstructive This is a fine classification for the clinician because it calls immediate attention to three basic pathogenetic mechanisms by which jaundice may occur, on the other hand it does have a defect in not recognizing that there usually are mixed mechanisms responsible for jaundice

CLASSIFICATION OF JAUNDICE
(Ducci)

Prehepatic	Hemolytic Nonhemolytic
Hepatic	Hepatocellular Hepatocanalicular
Posthepatic	Complete obstruction Incomplete obstruction

And finally there is this most recent classification which has been suggested by Ducci the terms of which are fairly obvious and which emphasizes the fact that jaundice may be the result of mechanisms which act prior to the bilirubin reaching the liver which act within the liver, or which act after the bilirubin has passed through the liver Included in the last of course, are the various types of obstructive jaundice One of the chief advantages of this classification is that for the first time there is emphasized the fact that hepatic jaundice may be the result not only of liver cell damage but of changes in the canaliculi the finest bile passages within the liver But this classification also suffers from failure to include any mention of mixed forms of jaundice in other words jaundice in which there might exist both obstruction and liver cell damage or hemolysis and liver cell damage

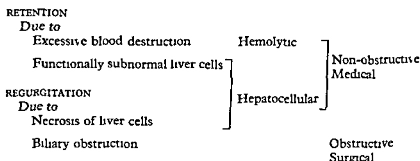
bilirubin and, finally, there may be some obstructive process which leads to disruption of the bile passages within the liver so that the bilirubin which has been excreted by the liver cells gets back into the general circulation in that way Therefore the essential processes which can lead to the development of jaundice are the overproduction of bilirubin, overproduction in the sense of this being beyond the capacity of the liver to excrete, a dysfunction of liver cells, a destruction of liver cells, or some type of biliary obstructive mechanism These various things can occur singly or in combinations of various types

CLASSIFICATIONS OF JAUNDICE

On the basis of the different steps in the pathogenesis of jaundice, there have been a number of classifications of jaundice

CLASSIFICATION OF JAUNDICE

(Adapted from Rich)



This outline is modified from the work of Rich and presents one of the standard classifications of jaundice I won t review it in detail except to point out some of the reasons why this classification does not have the wide application that we wish it had The terms retention and regurgitation jaundice are clear in their implications The latter implies the accumulation in the blood stream of bilirubin that has passed through the liver cells but gets back into circulation for various reasons When this particular classification was first introduced it was hoped that specific laboratory criteria would help in the differentiation of jaundice into these two categories Rich spoke about ' retention jaundice" as being characterized by the accumulation in the blood stream of indirect reacting bilirubin and the presence of an excessive amount of urobilinogen in the urine with an absence of bilirubinuria In "regurgitation jaundice the characteristic laboratory features about which Rich spoke were the accumulation in the blood of direct reacting bilirubin, and the presence of bilirubin and of varying amounts of urobilinogen in the urine We now know that these laboratory criteria are not so hard and fast as Rich implied and that differentiations that are based on them are apt to be somewhat incorrect But a chief difficulty that we find with this classification is the fact that it lists hepatocellular jaundice as being both retention and

icterus is the *previous history* of the patient particularly a history of previous attacks of pain Attacks of pain suggesting so called biliary colic, attacks of pain which in the past may have been associated with jaundice, indicate that the patient may now have a common duct stone A history of a previous, operation within relatively recent months, which involved the biliary tract, raises the possibility of common duct stricture, and, of course, a past history of a disease which required the administration of any of the blood products or any medication by injection suggests that homologous jaundice may now exist In the same category should be included a history of the administration of drugs which are known to be hepatotoxic, such as arsenicals, cinchophen etc Now, of course, these historical features are by no means entirely conclusive and we very often are led astray by them We recently had the rather sad experience of seeing a jaundiced patient who had been operated upon two or three months before and supposedly carefully explored and who had had blood transfusions at that time, two or three months prior to the development of jaundice, turn out eventually to have carcinoma of the pancreas as the cause of his jaundice There is no law that says that a patient who has gallstones cannot develop hepatitis or that one who has been given plasma cannot have cancer but in an over all picture of the case these various historical features are of tremendous importance

Another clinical approach to this problem is the history of the symptoms at the onset of the jaundice Of these *pain* is probably the one upon which we can place the most reliance It is true that severe hepatitis occasionally begins with pain and we know that once in a while a patient who develops severe necrosis of the liver has pain that is so severe that operation is performed in the thought that the patient has cholecystitis or cholelithiasis But that is not a very common thing and usually the jaundice that is a result of hepatitis is painless jaundice

On the other hand jaundice that is the result of gallstone disease is associated with pain or follows closely an attack of pain that is quite typical of so called colic in about 75 per cent of the cases In about 5 per cent of the cases gallstone jaundice is painless

Recent work has emphasized that in carcinoma of the pancreas, the jaundice is not usually painless that approximately 75 per cent of the patients who have carcinoma of the pancreas have pain as a major symptom, that if pain occurs in these patients it usually precedes the onset of the jaundice That is a very important feature to emphasize because it means that a patient who has painful jaundice will still be considered as possibly having carcinoma of the pancreas as a cause for jaundice but the reverse of this should be emphasized that carcinoma of the pancreas may also be a painless disease and produce jaundice without pain in some patients, and particularly that a small carcinoma at the head of the pancreas or close to the head of the pancreas can be free of pain for a relatively long period of time after jaundice has developed during which time detailed diagnostic studies have to be carried out

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THE BASIS OF DIFFERENTIAL DIAGNOSIS

Jaundice as a symptom may be due to a tremendous number of causes, and it would be very time-consuming to list all of the various things that can result in the development of jaundice in an individual patient In the experience of the average clinician what is necessary is to differentiate between jaundice that is a result of major biliary obstruction, such as jaundice due to obstruction of the bile ducts from stone, or carcinoma, or, less frequently, stricture, on the one hand, from jaundice that is caused by liver cell damage, either acute—from an infectious process, such as what we call viral or infectious hepatitis, or from drug injury—or a manifestation of chronic hepatitis, in other words, what is most commonly called cirrhosis In its simplest terms *the differential diagnosis of jaundice comes down to a decision as to whether* the jaundice is caused by something that we can treat medically or whether its cause is something that requires surgical intervention

The diagnostic aids to the differential diagnosis of jaundice are both laboratory and clinical Unfortunately, in recent years there has been a tremendous emphasis on the laboratory approach to the differential diagnosis of icterus, so much so that attention has been taken away from the numerous clinical features of a case of jaundice which are often of greatest importance in arriving at an accurate diagnosis It has been said, and I see no reason to disagree with the statement, that in about 80 per cent of the patients with jaundice it should be possible, on the basis of a careful history, competent physical examination and a careful consideration as to the degree of permanence of biliary obstruction as shown in the color of the stool, to reach a fairly accurate conclusion as to the nature of the problem involved That, of course, leaves a sizeable percentage of patients in whom more detailed information is necessary, but it emphasizes the fact that care and skill of an ordinary clinical nature are still paramount in the approach to this diagnostic problem

CLINICAL FEATURES

I would like to review some of the simpler clinical features that are important in a study of the jaundiced patient Many of them are very obvious The *age* of the patient is an extremely valuable diagnostic point We know on the basis of the statistics of jaundice that in childhood, in adolescence and in early adult life the most common cause of jaundice is the type of liver cell damage that is the result of acute liver cell injury from the various hepatitides We know that as patients get older, the incidence of mechanical jaundice, from stone in middle life and carcinoma in later life, *increases* The figures are by no means absolute, and certainly our recent experience indicates that hepatitis is occurring much more frequently in the older age groups than we thought twenty years ago For that reason it is an ever-present diagnostic problem even in the oldest person, but it is true in general terms that the older individuals are the ones in whom obstructive jaundice occurs

Another very important feature to recognize in the differential diagnosis of

icterus is the *previous history* of the patient, particularly a history of previous attacks of pain Attacks of pain suggesting so-called biliary colic, attacks of pain which in the past may have been associated with jaundice, indicate that the patient may now have a common duct stone A history of a previous, operation within relatively recent months, which involved the biliary tract, raises the possibility of common duct stricture, and, of course a past history of a disease which required the administration of any of the blood products or any medication by injection suggests that homologous jaundice may now exist In the same category should be included a history of the administration of drugs which are known to be hepatotoxic, such as arsenicals, cinchophen etc Now, of course, these historical features are by no means entirely conclusive and we very often are led astray by them We recently had the rather sad experience of seeing a jaundiced patient who had been operated upon two or three months before and supposedly carefully explored and who had had blood transfusions at that time, two or three months prior to the development of jaundice, turn out eventually to have carcinoma of the pancreas as the cause of his jaundice There is no law that says that a patient who has gallstones cannot develop hepatitis or that one who has been given plasma cannot have cancer, but in an over all picture of the case these various historical features are of tremendous importance

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jaundice, are particularly important when it comes to the recognition of infectious hepatitis, the high incidence of previous symptoms, the grippe like syndrome or the gastrointestinal upset that initiates hepatitis, is quite familiar to all clinicians In many forms of hepatitis, however, the jaundice occurs insidiously—the patient has no initial symptoms That seems to be particularly true of the homologous serum type in which jaundice develops insidiously with, very often, no other symptoms except anorexia, occasional itching and no other warning When prodromal symptoms do occur, however, they often are of great diagnostic assistance

In considering the clinical features which aid in the differential diagnosis of jaundice something must be said about the *degree of jaundice* and its *persistence* Jaundice that is due to stone in the common duct is ordinarily not very pronounced jaundice, and it usually doesn't last very long A patient who gets a stone in the common duct ordinarily reaches the peak of his jaundice in a relatively few days and then the jaundice tends to subside There will be fluctuations with gradual subsidence of the jaundice which may take a number of days, a week to ten days or more, but once the jaundice has reached its peak and begins to go down the rate of subsidence is usually not very slow When we see patients who have persistent jaundice, the question is always raised, could a stone in the common duct cause persistent and fairly constant jaundice of long duration? In my own experience that has been very, very unusual I've seen it in possibly two or three cases, but as a general thing the patient who becomes jaundiced and remains deeply jaundiced without much fluctuation over a period of weeks probably does not have a stone The persistent, pronounced icterus that doesn't fluctuate very much is usually due to either carcinoma of the pancreas or severe hepatitis, the type of hepatitis that is associated with the so called intrahepatic obstruction, the type of hepatocanalicular jaundice which is mentioned in Dr Ducci s classification Of these two, it is likely that icterus due to hepatitis will fluctuate over a little wider range than that due to carcinoma, but in both of these instances the degree of fluctuation may be very slight and sometimes it may be very difficult to tell simply on the basis of the degree and the persistence of jaundice which of these two entities is present, carcinoma or intrahepatic obstruction On the other hand, the jaundice that is the result of the usual type of hepatitis the hepatitis in which the hepatocellular damage is prominent and in which liver dysfunction is marked, usually reaches its peak within a week to fourteen days and may persist for a like period and then gradually subside, usually in a fairly steady and consistent, non-fluctuating manner

PHYSICAL FEATURES

Turning to the physical examination of these patients, we find that enlargement of the liver is so common in both the jaundice associated with hepatitis and that associated with biliary obstruction that the mere presence of hepatic enlargement does not help very much in differential diagnosis On the other hand, *splenomegaly* is an extremely important physical feature if it is demon

strated Enlargement of the spleen occurs in probably from 10 per cent to 30 per cent of patients who have the acute type of hepatitis that causes jaundice It occurs in probably 75 per cent to 80 per cent of the jaundice that is a result of cirrhosis The most important thing to say however about splenomegaly in the differential diagnosis of jaundice is that it occurs so seldom in patients with obstructive jaundice that when the icteric patient is found to have an enlarged spleen, that can be considered to be fairly good evidence that the mechanism of the jaundice is not some gross, extrahepatic obstruction

The other physical feature which requires mention of course is the demonstration of a *palpable gallbladder* Courvoisier s law is still a good law in the sense that distention of the gallbladder rarely occurs in the jaundiced patient unless the mechanism causing the jaundice is a malignant process at the head of the pancreas It is true that we see enlarged gallbladders in some patients who have gallstone jaundice but under those circumstances, the gallbladder enlargement is usually produced by inflammatory reaction and the gallbladder is tense and tender, and the enlargement is associated with a good bit of peritoneal reaction The distended gallbladder of the patient who has carcinoma at the head of the pancreas and jaundice, on the other hand, is a soft cystic mass that is not tender As a matter of fact, it may be very difficult to feel if we are too strenuous in our efforts at palpation The gallbladder is palpable in about 50 per cent of patients who have jaundice due to carcinoma at the head of the pancreas, or of the ampullary region The error there of course is in assuming that if the gallbladder is not pal pable carcinoma is not present a conclusion which is by no means justified

LABORATORY PROCEDURES

Of the various laboratory procedures that should be spoken about, one that is very often neglected is simple *inspection of the stool* In determining both the degree and duration of biliary obstruction, inspection of the stool, or the patient s statement about the color of the stool is an extremely important clinical guide The approach to the diagnosis of the cause of jaundice may be entirely different if we know not only that the patient has been jaundiced for a few weeks, but that his stool has been clay colored or did not contain obvious bile in that period of time Periods of acholia may occur in any form of jaundice, except the hemolytic variety Patients with gallstones may have acholic stools but if this does occur it is usually of short duration Patients with hepatitis may have acholic stools but that is also usually of a few days duration Acholic stools are observed for longest periods in the permanent obstruction due to carcinoma such as carcinoma of the pancreas and, of course acholic stools may be seen for longer periods of time as I ve already indicated in the patients who have the protracted types of intra hepatic obstruction from hepatitis

The various laboratory procedures that are used have added immeasurably to our knowledge of the differential diagnosis of jaundice What we are interested in at this time is chiefly the differentiation of obstructive jaundice

from the jaundice that is due to hepatitis A few words should be included, however, about the laboratory features of hemolytic jaundice

The important things to say about the laboratory features of hemolytic jaundice are these that it is the one type of jaundice in which there is no evidence of liver dysfunction and, in addition, it is a type of icterus in which there are associated very characteristic hematologic features This is the type of jaundice in which there is anemia, and in which the anemia is associated with reticulocytosis and a tendency to spherocytosis and an increase in the red blood cell fragility Fortunately, this differentiation does not have to be made very often, because by and large, at least in our own experience, the incidence of hemolytic jaundice is so small that we ordinarily are concerned primarily only in the differentiation between biliary obstruction and the icterus that is a result of liver disease

The laboratory differentiation of these two forms of jaundice depends largely on two facts first, the fact that liver dysfunction occurs relatively early in jaundice that is due to hepatocellular damage, and second, that obstructive jaundice, of course, is associated with interruption of bile flow

There are a number of things that have to be said in a negative way about the relative values of certain laboratory procedures in the differential diagnosis of jaundice One fact that needs to be reiterated, although it has been said many times before, is that the ordinary van den Bergh procedure is of no value in the differential diagnosis of these two types of jaundice Both of them give the so-called direct reaction, so that it is impossible on the basis of the ordinary van den Bergh technic to tell whether a patient has obstructive jaundice or jaundice that is a result of liver cell damage It is possible that, as time goes on and we learn more about measuring the amounts of direct reacting bilirubin in the blood stream, we may have some differential help here because it is true that generally there is a higher percentage of direct reacting bilirubin in the blood when a patient has obstructive jaundice than when he has jaundice that is due to liver damage At present, however, it would seem that the overlapping of these two groups is so great that not too much reliance can be placed on this particular procedure

Another test which has very little value in the differential diagnosis of jaundice is the bromsulfalein test The bromsulfalein test is of no value here because in both hepatocellular and obstructive jaundice there is dye retention, in one case because the liver cells have failed, and in the other case because of the mechanical difficulty in passing the bromsulfalein out through the bile ducts In any case, the bromsulfalein test is of little value in the study of jaundice except for those rare instances of hemolytic jaundice in which it can be said that bromsulfalein retention does not occur

The urobilinogen determination has certain limitations in the differential diagnosis of jaundice Characteristically, when bile flow stops, whether it stops because of mechanical factors or because the liver stops working temporarily insofar as the excretion of bile is concerned, bilirubin no longer reaches the intestinal tract and urobilinogen formation ceases Under those circumstances, urobilinogen will disappear from the urine That may happen

under a variety of circumstances It can happen if the patient has permanent obstruction obstruction from carcinoma, and it can happen if there is temporary liver dysfunction, such as occurs in hepatitis The important thing to say here is that single random determinations of urobilinogenuria do not have much diagnostic value If we determine on one or two occasions that there is no urobilinogen in the urine that does not prove that the patient has biliary obstruction and it does not tell us anything about the character of the obstruction Urobilinogen determinations are most important if they are done repeatedly over many days ten days, two weeks or even longer because it is extremely unusual for non malignant types of obstruction or even the moderately severe forms of hepatitis to persist without some bile flow during that period of time so that urobilinogen can be found Therefore, the chief value of urine urobilinogen determinations lies in determining urobilinogen repeatedly over long periods of time to see whether its absence is permanent

As I have already said, the characteristic laboratory feature of hepatocellular jaundice is the fact that liver cell damage occurs relatively early in its course This means that the tests which are based upon liver dysfunction like the galactose tolerance tests or the various flocculation tests or the hippuric acid synthesis have a tendency to be positive relatively early in the course of hepatocellular jaundice They are of value in differential diagnosis when they are done early in the course of jaundice because they are usually positive at this time There is no test that is uniformly positive in every patient who has liver cell damage jaundice These tests have a general diagnostic accuracy of possibly 80 per cent That is a very loose figure and I will not discuss it further at this time The important thing to say however, is that there are many patients who have liver damage in whom these tests are negative It is important to realize that by doing many tests and doing them repeatedly we have a greater chance of picking up liver dysfunction than if we do one test and do it only once

In obstructive jaundice on the other hand patients ordinarily do not have much evidence of liver damage early in the course of their jaundice That means that if we do tests like the ones that I have just mentioned relatively early in the course of mechanical jaundice, the results are ordinarily negative there isn t evidence of liver damage So that if we have a patient who has obstructive jaundice and we do a galactose tolerance test or we do a cephalin test or the thymol tests or the hippuric acid test, we are more likely to find these tests to be negative in obstructive jaundice They are positive in possibly 5 per cent of patients who have obstructive jaundice In other words, the differential between obstructive and hepatocellular icterus is great enough to be of definite diagnostic value

In addition there are certain tests which are valuable in demonstrating or suggesting, I should say, the presence of biliary obstruction In biliary obstruction there is usually increase in the amount of alkaline phosphatase in the blood and there is a tendency to hypercholesterolemia, and these findings may be of great diagnostic value When we have a combination of a negative response to tests like the galactose test and the cephalin test and an increase

in phosphatase, an increase in the total cholesterol and persistent absence of urobilinogen from the urine, we have a composite picture that strongly suggests that biliary obstruction is present

And then, of course, in addition there are certain specific tests that may be of value in telling us something about the nature of biliary obstruction when it exists It is important in the jaundiced patient in whom the suspicion of carcinoma of the pancreas is being entertained to do tests like serum amylase and lipase determinations because of the fact that an increase in the enzyme content, particularly the lipase, of the blood is frequent in patients who have carcinoma of the pancreas It is wise, in these patients, to determine the blood sugar, since hyperglycemia is common in patients with carcinoma of the pancreas It is also important to study the stools for occult blood, because the persistent presence of occult blood in the icteric patient means that a suspicion of carcinoma of the pancreas or common duct should be entertained And it very often is helpful under these circumstances to get detailed x-rays of the upper gastrointestinal tract to see whether pressure on the stomach or the duodenum from an enlarged pancreas can be demonstrated

The chief difficulties that we have are these That a great many patients don t have the characteristic clinical and laboratory features that we would like them to have The liver function tests are of great value when they are positive, when they are negative they do not exclude liver disease You have all seen patients who have had prolonged hepatitis in whom it has been difficult to determine this because the flocculation tests have been negative, because the urine has been negative for urobilinogen, because they have had a slight phosphatase increase and because they have had all or many of the laboratory features that we ordinarily associate with obstructive jaundice I, myself, am not completely convinced that liver biopsy will always make that differential diagnosis We hoped that it would, but so far there is not conclusive evidence that it does In these patients we very often are tempted to operate in an attempt to find the cause of the jaundice and sometimes we do have to operate before a definite diagnosis can be made

I think that in closing, however I would like to emphasize one point in the differential diagnosis of jaundice that is very often overlooked, and that is the importance of the passage of time It is true that in the majority of patients with jaundice we can make a diagnosis of the cause of jaundice early in the course by clinical observation and judicious use of the various laboratory procedures But there is no hurry about making a diagnosis of jaundice early, there is no rush about subjecting the patient to an operation for the purpose of diagnosis, there is no need to fear that something terrible will happen if the jaundice persists for a period of two or three weeks or more while we are watching the patient The important thing in these patients is to give ourselves enough time to follow the clinical course, to observe what happens to the jaundice, to see what happens to the liver function tests, to see whether the things that we think of at the beginning as evidences of malignant obstruction tend to disappear with a little time If we take time with

these patients and watch them carefully we very often will avoid subjecting individuals who have critical illnesses and who don t tolerate operations well to needless exploratory procedures with possible damage to the common duct and all of the various other tragedies that may follow unnecessary and injudicious biliary surgery

THE SO-CALLED POSTCHOLECYSTECTOMY SYNDROME

HENRY L BOCKUS, M D

According to reports from leading authorities approximately 80 to 90 per cent of patients subjected to cholecystectomy for cholelithiasis experience satisfactory results Not more than 50 per cent of patients subjected to cholecystectomy for so-called chronic non-calculous cholecystitis experience satis factory results It may be fair to say therefore that in the most expert hands one might anticipate something like 15 to 20 per cent of poor results following the operation of cholecystectomy

It is a little difficult to prepare a satisfactory classification of the causes of the postcholecystectomy syndrome which permits of an orderly presentation of the topic I shall try to discuss the principal issues involved under two main headings, but it is not possible to avoid some overlapping In the first group are included those patients who continue to complain of symptoms after cholecystectomy identical with those which had been present prior to operation In the second group are included those patients whose symptoms follow the operation and could actually be the result of operation

PERSISTENCE OF PREOPERATIVE SYMPTOMS

I should like to discuss under this heading four topics (1) erroneous pre operative diagnosis (2) residual undiscovered common duct stone, (3) disorders of the pancreas and (4) hepatitis and/or cholangitis In my experience the latter is an overworked diagnosis to explain the postcholecystectomy syndrome

ERRONEOUS PREOPERATIVE DIAGNOSIS

In the first category I should like to make merely a few comments It is very necessary for you and me to make sure of the diagnosis of chronic gallbladder disease before subjecting the patient to operation We should no longer accept such evidence as imperfect emptying of the gallbladder after a fat meal or a questionable lack of normal density of the gallbladder shadow by cholecystography In the latter instance the roentgen examination should be repeated before accepting equivocal evidence of disease as an indication for operation particularly in the absence of true biliary colic

Perhaps some of us had better get out of our minds the old fashioned dic tum that gallstone disease is the common cause of abdominal dyspepsia and gas, because it isn't The old axiom of the "belching female of fair, fat and forty has gallstones ought to be forgotten The average patient with biliary colic due to gallstones has one symptom which can be attributed to the gallstone disease, namely biliary colic, dyspeptic symptoms have no critical value in gallbladder diagnosis The most common cause of gaseous dyspepsia in my practice is not gallstone disease even though the patients have gall stones, it is aerophagy or colonic and intestinal dysfunction and gastro-intestinal neuroses

I think we should also keep in mind that even in the patient who has gallstone disease, other conditions may be present capable of causing symp toms Before the patient is sent to the surgeon we should analyze the mechan ism of the presenting symptoms carefully, making every effort to decide what proportion of the total subjective symptom picture is due to the presence of gallstones and what proportion is the result of other abnormalities which may be present The patient should be told before operation what degree of relief may be anticipated following the surgical procedure

Many patients with cholelithiasis are stout and either in middle or late life, they not infrequently have diabetes A large proportion of them have some type of cardiovascular abnormality Not a small number have hiatal hernia and a few of them unfortunately will have an unsuspected carcinoma of the pancreas or of the posterior wall of the stomach, some of them have peptic ulcer disease and a great many have colonic dysfunction Obviously none of those conditions will be cured by cholecystectomy Even though it is agreed that cholecystectomy is indicated, I think gallbladder operations would be in better repute if we as physicians and surgeons would attempt to explain, before the patient goes to surgery, that he may possibly have symptoms after the operation from spinal arthritis or spondylitis or from many of the other things that I have just mentioned

COMMON DUCT STONE

Common duct stone is a frequent accompaniment of cholelithiasis Doctor Mirizzi of the Argentine Republic has had an extensive experience with im mediate cholangiography performed at the time of cholecystectomy In his very large series of cases he has found that 26 6 per cent of patients, sub jected to operation for cholelithiasis, also had a stone in the common bile duct Crump in Vienna reviewing necropsy material some years ago found that 24 per cent of 325 patients who had gallstone disease had a stone in the common bile duct Many leading surgeons, who open the common bile duct for the slightest indication, report a finding of something under 20 per cent of stones in the common bile duct in their patients with cholelithiasis Based upon the foregoing statistics perhaps it would be fair to assume that even though the operations are performed by the *most expert surgeons*, approxi mately 5 per cent of our patients with cholelithiasis leave the operating table

with a stone in the common bile duct Certainly one would be justified in coming to that conclusion if the statistical error is not too great

Whether the inference is correct or not, I am not satisfied with the accuracy of present surgical methods for determining the presence of a stone in the common bile duct or for removing all stones and I know of no expert surgeon who is satisfied I wonder whether the time has not arrived when some consensus could be obtained concerning the best technic for determining the presence of stones in the common bile duct and for the best procedure to insure their complete removal Perhaps Mirizzi is right in claiming that, to be certain of the presence or absence of common duct stones at the time of cholecystectomy an immediate cholangiography must be performed At present this procedure is not commonly employed in this country According to Mirizzi the procedure does not increase the risk of operation It is my feeling that immediate cholangiography should be given further trial unless some other simpler technic is evolved for efficient exploration of the common bile duct Certainly intubation, suction and probing leave much to be desired I understand that Dr Ravdin is trying a plan which involves transmission of sound with instrumental contact with a stone We await further news of this new approach

Often the diagnosis of common duct stone in the postcholecystectomy patient presents little difficulty Typical attacks of biliary colic are followed by jaundice and in some instances chills and fever However in many patients who have attacks simulating biliary colic in the absence of recognizable jaundice, at varying intervals after cholecystectomy, the diagnosis may be difficult Cholecystography is rarely of value in this connection Biliary drainage is of pathognomonic value if one recovers calcium bilirubinate pigment and cholesterol crystals in the bile sediment Unfortunately our percentage recovery of those elements in common duct stone cases (following cholecystectomy) has not averaged much more than 20 per cent Wilkinson, in Boston has had greater success with recovery of these elements in his cases of choledocholithiasis However I think it is true that a definitive diagnosis cannot be achieved in the majority of patients with residual common duct stone by x ray and diagnostic biliary drainage

In many instances these patients are seen in the interim between attacks and all laboratory studies are negative I have made it a practice to instruct such patients to return to the office for *reexamination on the morning following a pain attack* At this time a serum bilirubin determination is carried out Hyperbilirubinemia occurring within twelve to twenty four hours after a pain attack is evidence favoring common duct stone Biliary dyssynergia is usually not accompanied by latent icterus Further information may be obtained by laboratory examinations carried out soon after a pain attack It has been my practice to include the determination of the sedimentation rate a leukocyte count serum amylase determination urinalyses for bile and urobilinogen and microscopy of feces to search for cholesterol crystals and calcium bilirubinate In quite a number of patients the decision for operation

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Many patients with cholelithiasis are stout and either in middle or late life, they not infrequently have diabetes A large proportion of them have some type of cardiovascular abnormality Not a small number have hiatal hernia and a few of them unfortunately will have an unsuspected carcinoma of the pancreas or of the posterior wall of the stomach, some of them have peptic ulcer disease and a great many have colonic dysfunction Obviously none of those conditions will be cured by cholecystectomy Even though it is agreed *that cholecystectomy is indicated, I think gallbladder operations* would be in better repute if we as physicians and surgeons would attempt to explain, before the patient goes to surgery, that he may possibly have symptoms after the operation from spinal arthritis or spondylitis or from many of the other things that I have just mentioned

COMMON DUCT STONE

Common duct stone is a frequent accompaniment of cholelithiasis Doctor Mirizzi of the Argentine Republic has had an extensive experience with immediate cholangiography performed at the time of cholecystectomy In his very large series of cases he has found that 26 6 per cent of patients, subjected to operation for cholelithiasis, also had a stone in the common bile duct Crump in Vienna reviewing necropsy material some years ago found that 24 per cent of 325 patients who had gallstone disease had a stone in the common bile duct Many leading surgeons, who open the common bile duct for the slightest indication, report a finding of something under 20 per cent of stones in the common bile duct in their patients with cholelithiasis Based upon the foregoing statistics perhaps it would be fair to assume that even though the operations are performed by the *most expert surgeons*, approximately 5 per cent of our patients with cholelithiasis leave the operating table

If adhesions are suspected because of the character of the symptoms such as a suggestion of intermittent mild intestinal obstruction or symptoms related to the intake of food or a postoperative alteration in bowel habit, barium meal and barium enema studies will be carried out If a roentgen abnormality is not detected, in most instances the symptoms are not due to adhesions

INJURY OR STRICTURE OF THE MAIN BILE DUCT

In introducing this topic I should like to repeat to you what a leading surgeon recently told me and which I have believed for many years i e, before a surgeon is allowed to do a gallbladder operation he should be a thoroughly expert abdominal surgeon I have been told by eminent surgical teachers that surgeons in training can learn to do a subtotal gastrectomy and a massive colectomy much more readily than they can handle the really difficult gallbladder operation It is important for clinicians to keep this in mind A common duct may be injured occasionally by the most expert surgeon in a difficult case in the presence of an anomaly of the blood vessels and of the ducts However indubitably the incidence of injury to the main bile duct is much greater in inexperienced hands In my opinion a chole cystectomy is one of the last operations a surgeon in training should be allowed to do

In some patients injury to the main bile duct is suspected because of the history Soon after operation a swelling may develop in the upper right abdomen or there may be an escape of large quantities of bile through the incision Signs of local peritonitis may appear jaundice may be the out standing feature When the immediate postoperative course is very stormy and objective findings suggest injury to the main duct with escape of bile, it is advisable to reoperate at once in order to avoid the dreaded complica tions of multiple adhesions and stricture always difficult to correct surgically

However patients with stricture of the main bile duct do not always give a clear history suggesting injury to the duct at the time Quite often the first symptoms of choledochal stricture may not appear until three or six months and, in some instances several years after cholecystectomy The first symptoms may be very mild simulating those of transient choledochal colic without jaundice Usually once a duct begins to stricture the condition is likely to be progressive The symptom of pain becomes more marked, jaun dice appears The duration of the jaundice with attacks increases and finally the patient may remain jaundiced Then it becomes necessary to utilize the tests mentioned by Dr Tumen to make sure that the jaundice is of the obstructive type If the diagnosis of obstructive icterus of the mechanical type can be made a prayer should be offered for the patient and for the surgeon, and another operation advised Reoperation for stricture following injury to the duct or from other causes may be exceedingly difficult A master surgeon who has had extensive experience with biliary tract surgery should be obtained

was made only after laboratory evidence obtained in this way favored the diagnosis of common duct stone I do not like to refer patients for a second biliary tract operation until I can be fairly sure that the symptoms are not on a functional basis Biliary dyssynergia will be discussed later

PANCREATITIS

A third diagnosis to account for a recurrence of symptoms following cholecystectomy is that of pancreatic inflammation Obviously pancreatitis may accompany biliary tract disease and may have been noted at the time of cholecystectomy If pain attacks simulating biliary colic follow cholecystectomy, residual choledochal calculus will be found to account for such attacks much more commonly than pancreatic inflammation Usually relapsing acute or chronic pancreatitis gives rise to attacks of pain of greater severity and much longer duration If recurrent pancreatitis is suspected, serum amylase and lipase tests should be performed as soon as possible after onset of pain The clinical importance of these tests in pancreatitis has been discussed previously

HEPATITIS AND CHOLANGITIS

In the past, one or the other of these two diagnoses has been made too often when in fact the postcholecystectomy symptoms have been due to a stricture of the common bile duct or a residual common duct stone Liver damage may be noted at the time of cholecystectomy in some patients who have had acute cholecystitis and/or severe jaundice with infection Residual hepatitis or cholangitis may occur in such patients However, neither of these conditions frequently accounts for the occurrence of biliary colic like attacks following cholecystectomy The clinical picture presented is more comparable to that found in chronic hepatitis or in chronic obstructive jaundice following stricture of the common bile duct

SYMPTOMS DEVELOPING POSTOPERATIVELY

The term postcholecystectomy syndrome, is perhaps more applicable to the second group of conditions to be discussed, since they develop actually as a result of the operation In this category are included (1) postoperative adhesions, (2) injury or stricture of the main bile duct, (3) disease of the cystic duct remnant, and (4) last and not unimportant, the removal of a functioning gallbladder

POSTOPERATIVE ADHESIONS

We will dismiss postoperative adhesions with a few words Postoperative adhesions are more likely to occur in those patients who have had badly diseased gallbladders, particularly in association with pericholecystitis, or in those in whom an actual rupture of the gallbladder has occurred, or in whom spilling of bile into the peritoneal cavity has occurred at the time of operation Ordinarily the "postcholecystectomy syndrome is not due to adhesions

If adhesions are suspected because of the character of the symptoms such as a suggestion of intermittent mild intestinal obstruction or symptoms related to the intake of food or a postoperative alteration in bowel habit, barium meal and barium enema studies will be carried out If a roentgen abnormality is not detected, in most instances the symptoms are not due to adhesions

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allow patients recently discharged from the hospital after removal of a functioning gallbladder to eat everything as some of my surgical friends seem inclined to do Many such patients if allowed to eat heavy fatty foods complain of postprandial dyspepsia and fullness gas belching and bowel irregularity, symptoms which may have been absent prior to operation Often such symptoms can be prevented by the simple admonition do not overeat, by the deletion of fat from the diet and by the administration of bile salts at the time of eating for some months after operation

In the dog several months after cholecystectomy, the physiologic behavior of the sphincter of Oddi may change Sphincter tonus returns and constant dribbling of bile no longer occurs It is likely that this change may also occur in at least some patients following removal of a functioning gallbladder When this does take place or when the sphincter fails to open following duodenal stimulation the ductal system may dilate somewhat and if non surgical biliary drainage is carried out a small amount of concentrated bile may be recovered It is conceivable that intraductal pressure may increase sufficiently at times to cause actual pain—a type of biliary dyssynergia

Pain of this origin I believe is likely to be of shorter duration than that of calculus colic, it may simulate that of angina pectoris Obviously in these instances all studies suggested for the discovery of choledochal calculus are instituted I have made this observation, which I believe has great practical importance Hyperbilirubinemia within eight to twenty four hours after the attack should be looked upon as favoring the diagnosis of choledochal calculus I do not recall having encountered hyperbilirubinemia in uncomplicated postcholecystectomy dyssynergia If biliary dyssynergia is suspected to explain the attacks, it may prove of interest to try the experiment of attempting to reproduce the spasm by giving a hypodermic injection of $^1/_6$ grain of morphine In some instances this may provoke an attack Nitrites may be prescribed for relief of the attack If morphine causes pain and nitrites relieve it the diagnosis of dyssynergia may be entertained Dr Kety, who will follow me, will discuss this very controversial topic of biliary dyssynergia at greater length and I am sure much more intelligently

SUMMARY

In closing I should like to reemphasize some phases of this important topic

(1) Do not subject the patient suspected of having chronic biliary tract disease to operation without objective evidence of such disease This is obtained principally by a carefully performed cholecystography You should have evidence that the gallbladder is diseased or that it contains stones, or that it doesn t concentrate bile (faint or no shadow) or there should be evidence of pericholecystitis Otherwise you had better continue the search for other possible causes for the patient s symptoms

(2) When you decide to send the patient for operation explain carefully to him what symptoms should be relieved by the operation and what symptoms will probably continue and require additional treatment Many of these patients have other disorders contributing to the total symptomatology

DISEASE OF THE CYSTIC DUCT REMNANT

This constitutes an occasional cause for the "postcholecystectomy syndrome" In 1887 Oddi reported the occurrence of dilatation of the cystic, hepatic and common bile ducts of animals following cholecystectomy I believe that Smythe and Hartman and Wood in this city, a number of years ago, discovered that if 6 mm of the cystic duct was allowed to remain in animals following cholecystectomy, it would *uniformly dilate* *It is known* that a long cystic duct remnant may dilate to the extent of forming a new gallbladder Peterson reported 27 such cases in 1932 A re-formed gallbladder will do just what an original gallbladder does It concentrates bile, it may become diseased, it may give rise to attacks of biliary colic as a result of stones or obstruction

It is well to keep this in mind since if the condition is suspected, chole cystographic study may cause the visualization of the new gallbladder or of the dilated cystic duct remnant Calculi may be visualized within the stricture I have not had that experience but several of my colleagues have In a recent number of Surgery, a surgeon from Charlottesville, Virginia, reported 9 cases of postcholecystectomy symptoms that were the result of disease of a cystic duct remnant Gray and Sharpe at the Mayo Clinic reported 44 patients with postcholecystectomy symptoms in whom cystic duct remnants were removed with relief of symptoms In 7 of the 44 cases, stones were present *in the cystic duct stump*

The finding of calcium bilirubinate or cholesterol crystals by non surgical duodenal drainage in the patient with postcholecystectomy symptoms is in dicative usually of calculi somewhere in the biliary tract

REMOVAL OF THE FUNCTIONING GALLBLADDER

I do not mean to criticize the removal of the functioning gallbladder because some patients who experience severe biliary colic attacks have a functioning gallbladder containing small stones However, it is essential to bear in mind that a physiologic readjustment must take place after removal of a gallbladder which has been functioning normally Its principal function is that of concentrating bile, thus reducing its total volume This activity together with changes in tonus of the sphincter at the lower end of the main bile duct regulates the pressure within the biliary ducts The gallbladder delivers to the duodenum its content of concentrated bile when it is needed to aid in digestion and absorption of fat Several investigators by animal experimentation have shown that following removal of a functioning gallbladder the sphincter of Oddi tends to remain relaxed, permitting a constant flow of liver bile into the intestine This tendency for recently secreted non-concentrated bile to dribble constantly into the duodenum evidently con tinues for some months Perhaps this is fortunate since it prevents the occurrence of pain attacks due to increased intraductal pressure However, during this period the ingestion of a meal containing fat is not followed by the entrance of a large amount of *bile into the intestine since there is no* reservoir from which bile can be withdrawn For this reason it is unwise to

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(3) Select a surgeon who is competent to perform the gallbladder operation if it turns out to be a difficult one

(4) The possibility of common duct stone must be always in mind at the time of original cholecystectomy The surgeon selected to perform the operation should be one who does not hesitate to explore the duct in the presence of recognized indications, or to do immediate cholangiography if other methods of excluding choledochal calculus are deemed insufficient Cholangiography before removing a common duct drain is a "must"

(5) If the patient returns after operation with postcholecystectomy symptoms reevaluate the whole story, get the report of previous operation from the surgeon, carry out the detailed studies which have been suggested Do not recommend reoperation until all non-mechanical causes have been excluded with certainty

(6) If you finally have to decide upon reoperation because of common duct *stone or stricture of the main bile duct from any cause, then be sure to* obtain the services of the master surgeon We are dealing here with a group of people, particularly those with common duct injury, who may have been subjected to a number of operations without relief and who eventually may die of biliary cirrhosis I was interested in the statement by Mr Maingot, eminent British surgeon, who visited here several weeks ago He said that he was particularly impressed during his visit to New York City by seeing posted for operation, during his brief stay there, twenty cases of common duct injury I am not stressing the occurrence of common duct injury in a critical way It is generally recognized that this accident occasionally occurs in the most competent hands I do believe that it is our duty as physicians to make sure that gallbladder operations are performed by competently trained surgeons in order to reduce the incidence of these unfortunate accidents

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THE PHYSIOLOGIST'S CONCEPT OF BILIARY DYSSYNERGIA

SEYMOUR S KETY, M D

By literal definition, biliary dyssynergia means a failure to act together, it is a lack of cooperation between certain parts of the biliary system Clinically,

it refers to that type of biliary disease in which the symptoms are due not directly to organic causes like stone inflammation or postoperative strictures, but simply to distention caused by spasm of the sphincter of Oddi

Perhaps a very brief description of the anatomy and the physiology of the gallbladder is in place at this time The gallbladder in man is a muscular organ capable of active contraction and, by its contraction capable of building up considerable pressure in the biliary system That portion of the common bile duct which lies within the duodenum the intramural portion, is also endowed with a definite circular muscular coat which constitutes the sphincter of Oddi In some individuals, and according to some observers, there is evidence of a sphincter at the tip of the gallbladder just as it enters the cystic duct The remaining portions of the hepatic cystic and common bile ducts in man have no muscular coat to speak of

NORMAL PHYSIOLOGY

Now let us turn to the normal physiology of this system Bile, as we know is secreted by liver cells into the hepatic ducts It is secreted at a pressure so that one can measure the maximum pressure which the cells of the liver can develop by the chemical process of energy transformation This maximum pressure has been found to be about 30 cm of water The production of bile by the liver is stimulated by the presence in the blood of bile acids or bile salts If the sphincter of Oddi is closed, which it normally is, the bile which is secreted by the liver has no other place to go but into the gallbladder where it is very rapidly concentrated to one fourth to one tenth of its original volume In this manner the gallbladder can accommodate the twelve-to twenty four hour output of the hepatic cells In addition the gallbladder secretes and excretes a small volume of its own materials into the bile which is in it, this amounts to about 20 cc per day

The gallbladder normally is not a static organ It is continuously in motion with a normal tonic rhythmicity of about one to four per minute These contractions may exceed pressure differences of several centimeters of water Occasionally in normal individuals the gallbladder may spontaneously contract and expel as much as one third of its contents even though the individual is fasting Generally however the gallbladder evacuates only in response to a certain stimulus and that stimulus as we know is a fat meal Ivy has recently isolated the hormone which is responsible for gallbladder contraction and this hormone he calls cholecystokinin This hormone is elaborated by the cells of the duodenal mucosa when they are stimulated by the presence in them of fat or of a high degree of acidity or of partially digested proteins A fat meal then causes the gallbladder to contract simply because the fats stimulate the mucosa of the duodenum causing the formation of cholecystokinin which is liberated into the blood stream, finds its way to the gallbladder and causes the gallbladder to contract Carbohydrates in the duodenal contents will not cause gallbladder contraction Cholecystokinin has been isolated by Ivy in a rather impure form when it is injected intravenously it produces a definite rapid evacuation of the gallbladder Thus

(3) Select a surgeon who is competent to perform the gallbladder operation if it turns out to be a difficult one

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was supposed to combine the analgesic effects of morphine with the antivagal or the antispasmodic effects of atropine In this case demerol acts like morphine and very little like atropine in fact recent work published only this year indicates that demerol is quite capable of producing practically the same intensity of spasm of the sphincter as is morphine Finally, there are some reflexes which may initiate sphincter spasm the only one which has been experimentally studied and observed is the colic reflex or distention of the colon in which experimentally it is possible to show a tremendous increase in tone of the sphincter of Oddi

Now how about the other side of the picture? What are the factors which reduce the tone of the sphincter of Oddi and therefore relax that structure? These are a fat meal cholecystokinin and then certain drugs The drugs are those which paralyze the parasympathetic system such as atropine and various newer synthetic preparations which have atropine-like properties, or amyl nitrite and nitroglycerin which relax all smooth muscle or theophylline ethylenediamine commonly referred to as aminophylline or magnesium and sodium sulfate all of these substances appear capable of relaxing the sphincter of Oddi

PRODUCTION OF DYSSYNERGIA

Normally, therefore we have a reciprocal action between the gallbladder and the sphincter When the gallbladder is empty the sphincter closes and the gallbladder gradually fills when the gallbladder contracts the sphincter opens and allows the gallbladder contents to be discharged normally into the duodenum What happens if this uniform cooperation is disturbed? What happens if the gallbladder contracts and at the same time the sphincter of Oddi contracts? Under those circumstances the contraction of the gallbladder produces a high pressure in the biliary system and we get this condition known as dyssynergia because the two mechanisms are no longer acting in cooperation with each other but rather in antagonism

There are two types of biliary dyssynergia one of which depends upon the presence of the functioning gallbladder However, there is another type which Dr Bockus has already described to you which exists in the absence of the gallbladder—which may in fact be aggravated by the absence of the gallbladder since the gallbladder normally acts as a reservoir or buffer mechanism to take up the pressure in the bile ducts until the gallbladder becomes considerably distended If this buffer mechanism is removed there is no other mechanism initially in the bile ducts to take up pressure if the sphincter should suddenly decide to close and therefore, in the removal of a functioning gallbladder one would expect to see an increased possibility of biliary dyssynergia It is true that the biliary ducts dilate following removal of a gallbladder and this dilatation in some individuals may be large enough to equal the volume which the gallbladder originally contained Is there any evidence that this simple process of increased pressure in the biliary system due to an unrelaxed sphincter of Oddi will in itself cause discomfort and pain without the intervention or mediation of inflammation stone or strictures?

occurs in two steps there is first an increased rate and amplitude of the normal tonic rhythmicity of the gallbladder, and superimposed upon this there is a gradual sustained compression of the gallbladder as a whole with the evacuation of its contents into the cystic duct, the common duct and finally the duodenum if the sphincter of Oddi is open or if it relaxes at the time that the gallbladder contracts

Now is there any reflex control to gallbladder contraction? That question is open in man, no one seems to know whether the autonomic nervous system has anything to do with the contraction of the gallbladder In the dog, however, stimulus of the vagus or the splanchnic sympathetics does not cause any movement of the gallbladder or any emptying

Magnesium sulfate, contrary to what is sometimes thought, does not cause the gallbladder to contract but simply opens the sphincter of Oddi and allows bile to drip out into the duodenum under the normal pressure which exists in the biliary system Now when the gallbladder contracts it exerts a pressure of some 25 cm of water which, you recall, is just a little less than the secretory pressure of the liver This may be a safety mechanism on the part of nature so that the gallbladder is not normally capable of squeezing bile back into the liver against hepatic pressure

FACTORS AFFECTING THE SPHINCTER OF ODDI

Now let us turn to the sphincter of Oddi Normally this resists the flow of bile, causing its storage in the gallbladder However, when the gallbladder contracts the sphincter dilates, permitting the gallbladder to discharge its bile into the intestine Cholecystokinin, the same hormone which causes gall bladder contraction, very fortunately also causes the sphincter of Oddi to relax The sphincter, in opposition to the gallbladder, is quite definitely under the influence of the autonomic nervous system, the vagus constricts the sphincter and the sympathetic nervous system appears to cause relaxation Under abnormal conditions, the sphincter of Oddi may remain closed in such a state of spasm as to produce considerable resistance to the passage of bile through it This resistance has been measured in man and found to be as high as 60 to 80 cm of water—considerably higher then than the pressure that can be developed either by the gallbladder contracting or by the secre tion of the hepatic cells, or indeed by both of them put together

Now what are the factors which increase the constrictor tone of the sphincter? What are the factors which cause spasm of the sphincter of Oddi? These are inflammation of the ampulla or the ducts, and also conditions which follow the removal of a gallbladder in man, probably the result of surgical trauma In addition, there are a number of drugs which increase the tone of the sphincter of Oddi and cause an aggravated spasm of that structure First of these drugs is pilocarpine Pilocarpine is a parasympathomimetic drug, it acts in the same way that the vagus acts upon the sphincter and therefore pilocarpine causes sphincter spasm Morphine also causes spasm of the sphinc ter of Oddi, as does codeine and also, disappointingly enough, so does demerol You will recall that demerol was developed as a synthetic preparation which

Chronic Ulcerative Colitis

Let me recite some of the experimental evidence In human subjects with a T-tube in the common duct, pressure can be increased simply by forcing saline into the T-tube and an increase in pressure of from 15 to 50 cm of water causes a typical biliary colic One group of workers produced typical biliary colic in 97 per cent of patients in whom they suddenly induced a pressure of 50 cm of water in the biliary system A pressure as high as this is certainly possible if the hepatic secretory pressure and the gallbladder pressure were to be added Secondly, Westphal did an interesting experiment He passed a duodenal tube and introduced olive oil and got a flow of bile The sphincter dilated normally and the patient was perfectly comfortable He then injected pilocarpine which, as we said before, constricts the sphincter of Oddi This was very soon followed by biliary colic and at the same time the flow of bile stopped The evidence is pretty good, then, that the pilocarpine constricted the sphincter, the bile no longer got out, and as a result of the pressure which developed in the biliary system, signs of biliary colic appeared He then gave the patient an injection of atropine, the flow of bile started again because atropine is a perfect antidote to pilocarpine, and the symptoms of discomfort and dyssynergia disappeared

Von Bergman did an experiment in human beings in which he gave intravenous dehydrocholic acid This caused an increased secretion of bile by the liver and if that occurred in normal individuals nothing happened, but if the same injection was given to patients who had stenosis of the common bile duct, that injection alone, which simply increased the production of bile, caused symptoms that were highly suggestive of biliary tract pain Then there is the very frequent clinical observation which Dr Bockus has mentioned, that patients after cholecystectomy who are given small doses of morphine may develop biliary colic This must be due to the fact that morphine is constricting the sphincter, increasing the pressure in the system and since there is no gallbladder, the pressure has nothing else to do but to dilate the duct and cause pain

SUMMARY

In summary, then, whenever the sphincter of Oddi remains closed in the face of a high pressure from the contracting gallbladder, or a high pressure due to continued secretion by the hepatic cells the pressure in the biliary system rises and this pressure alone in these cases is sufficient to account for the symptoms of biliary colic and discomfort This abnormal spasm of the sphincter may occur as a result of reflexes from the distended colon It may result from inflammation of the ducts, or following operation upon the biliary system, or it may result from certain drugs These drugs are morphine, codeine, demerol and pilocarpine, which therefore would be contraindicated to relieve the pain of biliary dyssynergia This spasm, on the other hand, may be relieved by the use of other drugs—atropine, amyl nitrite nitroglycerin and aminophylline—and, therefore, from the medical point of view these drugs may well be indicated in the therapy of this very interesting syndrome

LYSOZYME (MUCOLYTIC ENZYME) ACTIVITY IN CHRONIC ULCERATIVE COLITIS, WITH A PRELIMINARY REPORT ON ANTILYSOZYME THERAPY*

JOHN F PRUDDEN, M D, AND KARL MEYER, M D, PH D

Lysozymes are bacteriolytic enzymes widely distributed in animal tissues and in plants Human lysozyme and those from the lower animals are remarkably similar in their chemical properties, but they are not identical This can be demonstrated by various technics [1] Fleming gave this group of enzymes their name and worked with them for a time in hopes of developing an effective antibiotic It was soon realized that lysozyme was only bacteriolytic for saprophytes [3] The lysis of these saprophytes was shown[4] to be due to the hydrolysis of a mucoid element of the cell wall This element has been isolated and used in a viscosimetric quantitative determination of lysozyme in body tissues and juices [5] One unit of lysozyme is defined as that amount which will reduce the viscosity of a 0 4 per cent solution of this substrate to half viscosity in ten minutes under standard conditions

The enzyme has been found to be in highest concentration under normal circumstances in the tears, and in the mucosa of the gastric antrum pylorus and the first part of the duodenum [1] This localization in the alimentary tract led us to investigate its possible role in the pathogenesis of peptic ulcer The findings in the peptic ulcer study are reported elsewhere [1] The superficial similarity between peptic ulcer and ulcerative colitis prompted an investigation into the lysozyme content of the stools of patients with the latter disease After very large concentrations had been noted a more complete investigation was begun We will report the results of this work today

RESULTS OF ASSAYS

There is no necessity of going into the technical details of the laboratory methods for stool lysozyme assay These may be found elsewhere [6]

Table 37 shows the individual results of the assays in the study The normal stools have a mean of 2 7 units/gm The individual determinations were quite uniform Normal stools after purging with magnesium sulfate or castor oil showed only dilution of the enzyme, and averaged 1 6 units/gm Chronic ulcerative colitis stools exhibited a very great increase in the lysozyme content The mean in this group was 73 6 units/gm Only one titer over

* This study was supported in part by the Josiah Macy Jr Foundation New York N Y and the Research Grants Division of the U S Public Health Service

Table 38 indicates the determinations made on regional enteritis patients These data have been reenforced by additional cases, and the mean titer has remained about 16 units/gm

Table 38

SOURCE	INDIVIDUAL TITERS (UNITS/GM OF WET WEIGHT)			MEAN TITER
Regional enteritis (6 cases)	30 0 12 2	7 0 42 6	0 2* 6 9	16 5

* Three years postileocolectomy persistent watery diarrhea no blood or excessive mucus
(Meyer K et al in Am J Med Vol 5 Oct 1948)

Table 39 shows the tabulated twenty four hour fecal output in patients with colitis and in normal persons We see that there is an even more striking difference here than there was in the enzyme concentration of the stool the increase in the twenty four hour output being 168 fold over the normal daily

Table 39

SOURCE	INDIVIDUAL OUTPUTS 24 HOURS (UNITS)				MEAN OUTPUT (UNITS)
Normal stools	39	528	27 5	39 5	158
Normal stools after purging	647 879	18 3 582	1940 3000	380	1064
Chronic ulcerative colitis stools	44 000 22 563 59 024	328* 2080	64 500 39,200	4720 1950	26 568
Regional enteritis	16 750				

* In healing phase clinically
(Meyer K et al in Am J Med Vol 5 Oct 1948)

output An increase after purging is noted which contrasted with the decrease in concentration after catharsis This probably is due to the lack of inactivation of the enzyme which occurs in normal stools when the fecal matter remains in the rectum for variable periods of time Regional enteritis has continued to approximate the figure in this chart

Figure 236 is a graphic representation of the lysozyme concentrations in the various types of situations studied

lapped the control group (4 1) The diagnosis here was not clearcut, but the clinical impression was chronic ulcerative colitis, it was therefore included in this group Surface mucus from the rectosigmoid of patients with chronic ulcerative colitis exhibited very high titers, averaging 158 1 Stool titers from colitis patients clinically in remission were increased over normal stools, but

Table 37

SOURCE	INDIVIDUAL TITERS (UNITS/GM WET WEIGHT)*			MEAN TITER
Normal stools	0 5	9 4	4 4	2 7
(6 cases)	0 2	0 8	0 9	
Normal stools (after purging with $MgSO_4$ and	0 4	3 9	1 0	1 6
castor oil)	0 8	1 3	0 1	
(8 cases)	1 6	3 8		
Chronic ulcerative colitis stools	28 3	48 7	22 3	73 6
(32 cases)	49 0	10 5	180 9	
	33 3	47 0	103 7	
	24 2	119 4	4 1	
	35 0	25 0	46 0	
	49 8	125 0	125 0	
	84 0	20 0	160 0	
	86 5	18 5	9 8	
	109 6	22 3	87 0	
	78 2	40 0	39 2	
	21 8	502 0		
Surface mucus from rectosigmoids of chronic	43 5	80 0	15 7	158 1
ulcerative colitis patients	167 0	466 0	176 5	
(6 cases)				
Chronic ulcerative colitis stools clinically in remission	10 8	1 0	17 1	9 6
(3 cases)				
Ileal stools from individuals with C U C	0 1	2 0	3 6	2 8
(3 cases)				
Stools from patients with carcinoma of rectum much mucus	0 9	2 7		1 8
(2 cases)				
Idiopathic diarrheas with much mucus	0 1	1 0	5 0	2 1
(3 cases)				

* Each individual titer represents the lysozyme content of a stool specimen from a different person
(Meyer K et al in Am J Med Vol. 5 Oct 1948)

quite low in comparison with the titers in active disease Ileal stools from patients who had had diversion of the fecal stream had a normal content Specimens from patients with carcinoma of the rectum who had a great deal of mucus and from individuals with mucous colitis showed no increase in lysozyme content

Figure 237 shows 5 patients who were under treatment with nisulfazole a drug we shall discuss in a moment The arrows indicate the start of therapy

Table 40

	TYPE OF MUCOSA	INDIVIDUAL LYSOZYME TITERS				MEAN TITER	REMARKS
1	Normal colon	4 1 3 3	3 5 3 0	3 0 10 0	8 0	5 0	Specimens from uninvolved areas of colons resected for carcinoma
2	Biopsies from rectosigmoids of acute C U C patients	42	40	54	34	42 5	All of these cases had an acute exacerbation at time of biopsy rectal involvement proven sigmoidoscopically
3	Mucosa from resected colons in quiescent state following ileostomy or colostomy more than 6 mo previously	10 11 4	5 4	6 5	8 3	6 2	Although these colons were extremely fibrotic necessitating resection there was no rectal discharge or other evidence of activity at time of resection
4	Normal ileum	6 4	5 4	3 5		5 1	From ileums resected for malignancy
5	Ileum with regional enteritis	33 0					This patient had ileocolectomy for regional enteritis there were ulcers in ascending colon also
6	Ileum proximal to regional enteritis	18 0	13*			15 5	From item No 5 and another where side tracking ileocolostomy was done
7	Ulcerated colon in regional enteritis		5 4*				Specimen was from near an ul eration
8	Ileum proximal to retrograde involvement by C U C		12				The ileum had the characteristics of regional enteritis
9	Normal appearing ileum with entire colon involved by C U C		3 5				

* Specimens from the same patient with regional enteritis
(Meyer K et al in Am J Med. Vol. 5 Oct 1948)

You will notice that in every instance where there was improvement, the titer fell This very limited amount of data has been reenforced since this

Table 40 shows the mucosal assay results The table is self-explanatory The case starred in boxes 6 and 7 in this table is especially interesting An ileocolectomy was done for regional enteritis, and the ascending colon was found to be ulcerated on pathologic examination As shown in the table the involved ileum had a high titer while that of the colonic mucosa adjacent to an ulcer was normal There was a definite lack of the inflammatory changes one would expect in an ulcerated colon We interpreted this to mean that lysozyme in high concentration flowing over a mucosal surface can produce ulcerations without an inherently high lysozyme content The ulcerations

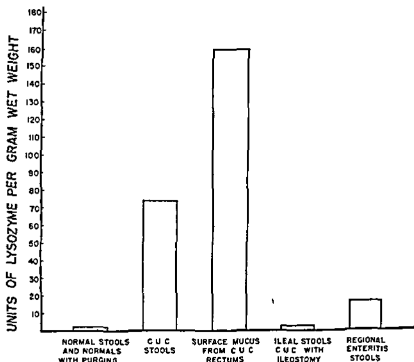


Fig 236 A comparison of the mean lysozyme titers in four groups studied (Meyer K et al in Am J Med, Vol 5 Oct 1948)

produced in the canine feeding experiments which will be discussed presently were of this type

One case of acute amebic colitis and one case of non tropical sprue were assayed The amebic colitis specimen contained 38 units/gm Amebae themselves were demonstrated in a semiquantitative run to contain appreciable amounts of lysozyme, and we tentatively assume this to be the mechanism of their pathogenicity Further work must be done on this problem The sprue case had a normal titer Further evidence that lysozyme plays an etiologic role in the pathogenesis of chronic ulcerative colitis is provided by a number of serial lysozyme assays on patients undergoing remission or exacerbation of their disease

Figure 238 shows the serial twenty-four hour lysozyme output rather than the concentrations The same fall with improvement and rise with relapse is demonstrated

HISTOLOGIC EXPERIMENTS

If lysozyme were to be assumed an etiologic rather than a corollary factor in the disease it was necessary to test our concepts histologically This was done first by determining if lysozyme as postulated, removed the surface mucus of the mammalian alimentary tract A Pavlov pouch was constructed and after complete healing had taken place, a solution of lysozyme in a concentration of 7500 units/cc was allowed to drip in over a four hour period Three hundred fifty cc entered the pouch in this time The pouch was then



Fig 239 Antral mucosa from Pavlov pouch after instillation of lysozyme in pooled human gastric juice Note cystic dilation of gastric glands (Meyer K et al in Am J Med Vol 5 Oct 1948)

removed in toto and fixed without handling The result is shown in Fig 239 By contrast the normal canine gastric mucosa is shown in Fig 240 The complete absence of surface mucus in one slide and its abundance in the other is apparent

The second step was to investigate the effect of daily ingestion of large amounts of lysozyme on the intact alimentary tract of the dog Seven feeding experiments ranging in length from three and a half days to thirty eight days and in daily dosage from 10,000 to 800 000 units have been carried out In every instance there has been superficial epithelial sloughing and necrosis as well as a characteristic decrease in the surface mucus In every experiment but one there have been at least one and usually three to six ulcerations which were visible grossly Microscopically these involved from the super-

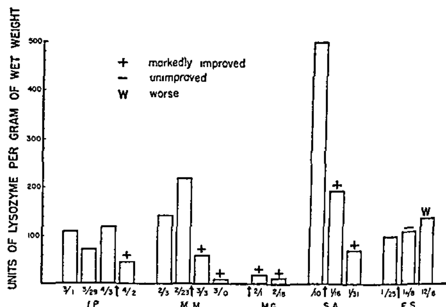


Fig 237 The correlation between clinical status and the lysozyme content of the stool, nisulfazole therapy begun in the intervals indicated by arrows (Meyer K et al in Am J Med Vol 5 Oct 1948)

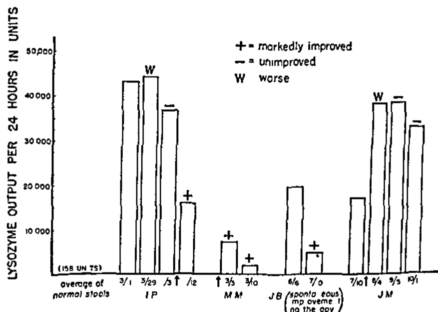


Fig 238 Nisulfazole therapy begun in the intervals indicated by arrows (Meyer K, et al in Am J Med Vol 5 Oct 1948)

slide was made, and the additional cases all fit into the same pattern The titer rises when the patient is worse, falls as he improves

because of the so called pseudo ulcers which occur in the small intestine of about 70 per cent of canine guts It is felt that these areas are probably sites of diminished resistance because of certain histologic effects noted in these experiments These studies will be completely reported soon

One of the best ulcerations obtained in these experiments is shown in Fig 241 This lesion was produced in the terminal ileum by the feeding of 270,000 units twice a day for three and a half days in a dog weighing 5 7 kg The terminal ileum at the site of this lesion was fiery red From these histologic studies it was concluded that lysozyme in high concentrations removes the surface mucus of the canine gut and permits ulceration of the mucosa by enteric and/or bacterial proteolytic enzymes

ACTION OF NISULFAZOLE

Successful treatment of chronic ulcerative colitis with nisulfazole (2 [p-nitrobenzene sulfonamido] thiazole) has previously been reported by Major [5] Dr Gellhorn[6] undertook therapy with this compound when it was found that it inhibited lysozyme A number of other compounds were screened for inhibition at this time Nisulfazole and the higher alkyl sulfates were the only ones exhibiting significant inhibition A 10 per cent suspension of nisulfazole in pectin* with oil of peppermint as a preservative was employed in therapy Retention enemas of 50 to 100 cc were given twice a day In the therapy of 21 patients, there was coincidental improvement in 13 no improvement or progression of symptoms in 6, and equivocal response in 2 They have been followed from six to twenty months The improvement was evidenced by decreased frequency disappearance of blood in the stools and increased weight and appetite However at the conclusion of therapy with nisulfazole, there was usually no significant improvement in the sigmoidoscopic picture If the improvement was held then healing of the ulceration and decrease of the edema and friability were noted Of the 13 nisulfazole treated patients who definitely improved 6 have held their improvement for a period of about a year Two have relapsed and the remainder have not been followed

Since chronic ulcerative colitis is characterized by spontaneous remissions and exacerbations we hesitated to attribute the improvement to nisulfazole but we do think that the results have been sufficiently encouraging to warrant further clinical trial of this preparation

Nisulfazole was tested for inhibition of lysozyme in a concentration of 0 0007 M, the limit of solubility At that concentration it was found to exert an inhibition of 42 per cent The mechanism of this inhibition is not yet known

THE ALKYL SULFATES

The use of an anionic detergent as an inhibitor was suggested by the very basic nature of egg white and mammalian lysozyme The most effective inhibitors were found to be the normal alkyl sulfates† from C 10 to C-18

* Generously supplied by the George A Breon Co of Kansas City Mo

† The Fine Chemicals Division of the E I duPont Co kindly furnished these compounds



Fig 240 Normal canine gastric mucosa from a portion of the stomach not connected with the Pavlov pouch Note the presence of surface mucus (Meyer, K, et al in Am J Med Vol 5 Oct 1948)

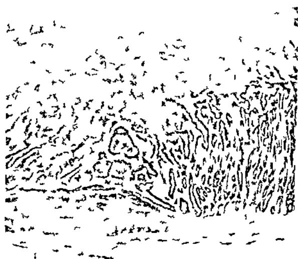


Fig 241 Deep ulceration of the terminal ileum of dog The necrosis penetrates the entire thickness of mucosa and is accompanied by an intense round cell infiltration (Meyer K et al in Am J Med Vol 5 Oct 1948)

ficial third up to the full thickness of the mucosa These ulcerations were noted from the cardia to the anus, but were most frequent in the small intestine Some difficulty has been encountered in interpreting some lesions

in detail One consideration which should be mentioned is that, being an anionic detergent, sodium hexadecyl sulfate acts by combining with the NH_3^+ groups of lysozyme Since lysozyme is the most basic mammalian protein thus far isolated, it has an abundance of these groups and the alkyl sulfate readily combines with it There are many other such groups available in the alimentary tract, however, and to minimize the possible reduction in inhibitory activity through this non specific reactivity we have prescribed low protein diets in the therapy with this compound. Further work is desirable to prove the necessity (or lack of it) of this measure Studies have indicated that there is no reduction in the inhibitory effect of sodium hexadecyl sulfate when solutions of the commercial casein hydrolysate Amigen are placed with it We therefore now give 15 gm of oral Amigen three times a day in tomato juice to compensate for the restriction of protein to 50 gm per day

Another fact should be recorded This is the circumstance that 3 of the 9 patients who responded to treatment with a remission experienced relapse in from one and a half to sixteen weeks after treatment was stopped This is not thought to be prejudicial to our concepts In treating this disease with an antilysozyme we are only attempting (if our conclusions are correct) to nullify the local effect of a systemic derangement, presumably of psychiatric origin Unless the fundamental mechanism of lysozyme production (at present unknown) has been altered in a non specific way during the hospital stay, exacerbation will occur when the inhibitor is removed It is interesting to note that 2 of the 3 relapsed patients are doing well at home on maintenance dosages of sodium hexadecyl sulfate

If lysozyme is an etiologic agent in this disease, the direct method of treatment will be to devise a means of influencing the mechanism of its production, once the latter has become evident

SUMMARY

The feces of individuals with chronic ulcerative colitis exhibit a striking increase in lysozyme content over that of normal stools and the increase in the output of the enzyme in the disease is relatively greater than that in the concentration The stools of regional enteritis patients show a similar, although less sizable increase in lysozyme titer Mucosal specimens from chronic ulcerative colitis and regional enteritis show a similar grade of increase over that of normal mucosa With clinical improvement the titers and daily lysozyme outputs fall Lysozyme will remove the surface mucus of the intestinal tract of the dog under various experimental circumstances In the amounts employed thus far it invariably has produced superficial mucosal necrosis in the intact alimentary tract of the dog All but 1 animal of 7 given lysozyme in capsules exhibited definite focal ulcerations Antilysozyme therapy of chronic ulcerative colitis with sodium hexadecyl sulfate and nisulfazole has been beneficial in most instances Therapeutic experimentation with these agents on a large scale is indicated The fundamental mechanism of lysozyme production has not yet been elicited These observations appear to

The maximal inhibition is reached at C-16 In a concentration of 0 0001 M the C-16 compound, (sodium hexadecyl sulfate) inhibits to 85 per cent This is a very effective inhibition

The lysozymes of human tears, gastric juice, saliva, etc , were all inhibited by the alkyl sulfates to the same extent as was egg white lysozyme, however, chronic ulcerative colitis stools were not The reason for this discrepancy became apparent when a 1/20 dilution of serum was added to a typical inhibition experiment and it was found that the inhibition was decreased about tenfold This would be expected as proteins other than lysozyme combine with the compounds, thus competing with the enzyme Lysozyme has an isoelectric point of 11 It therefore contains many free NH_3^+ groups and is "preferred by the detergent

We have recently been employing the C-16 compound clinically The dosage is 600 mg to 1 gm every four hours by mouth The patients have usually experienced moderate epigastric fullness and occasional nausea on the first one to two days of therapy This has characteristically disappeared, but one patient continued to complain of these symptoms throughout treatment The last four patients have also received concomitant retention enemas of 100 cc of a 0 025 M suspension of sodium hexadecyl sulfate twice a day Fourteen cases have been treated Nine cases have shown clinical remission By remission is meant a return to formed or semi-formed bowel movements, a frequency not exceeding three bowel movements per day, complete healing of the lesions seen at proctoscopy, and a definite fall in the lysozyme titer Unless all four of these criteria were met, the result was not classified as a remission The pre-treatment lysozyme concentrations in this group averaged 56 units per gram, and the daily output before therapy averaged 58,000 units per day, post-treatment they averaged 16 units per gram and 5000 units per day Three cases showed definite improvement with a fall in the frequency from 10 to 20 B M s/ day to 3 to 6 daily However, the stools did not become formed and were not always semi-formed although the consistency did improve In these cases the proctoscopic appearance became good, although 1-plus guaiacs remained in one patient The lysozyme titers fell from an average of 55 units/gm pre-treatment to a post treatment mean of 24 units/gm These cases are classed as improved but not as remissions

Two patients were not improved Their frequency was not significantly altered and their lysozyme titers did not fall It is interesting that these two patients exhibited the highest titers of the group, averaging 390 units/gm Presumably an insufficient amount of the alkyl sulfate was furnished to inhibit their intestinal lysozyme One patient was not proctoscoped for psychiatric reasons, the other s rectal mucosa displayed no significant improvement

It is felt that this is a good preliminary record with this drug A much larger number of cases will be necessary to place the clinical value of anti-lysozyme therapy on a sound statistical footing It is anticipated that better results will be obtained as more is learned about optimal dosages and modes of administration The therapeutic aspect of the problem will soon be reported

PRINCIPLES INVOLVED IN NITROGEN BALANCE STUDY

It may be assumed that practically all of the nitrogen concerned in the body metabolism is ingested in protein Hence for the purposes of this type of investigation protein metabolism can be measured as nitrogen metabolism and protein balance measured as nitrogen balance We measured the amount of nitrogen given these patients orally as food and by vein as amino acid hydrolysates blood and plasma Also the amount of nitrogen excreted in the urine as well as that in the stools was recorded We could thus compare intake and output of nitrogen

I think it s important to point out that there are certain conditions which must be satisfied if these studies are to be of significance Cardiorenal function must be adequate, otherwise a falsely low urinary nitrogen figure is obtained Recent surgery, as well as acute infections, will alter nitrogen metabolism for a variable period after the episode In pregnant patients and in children the protein requirements are abnormally raised and a positive nitrogen balance is obtained

The total protein intake should be relatively constant In normal individuals there may be as much as a two week lag in the excretion of extra protein as nitrogen after the diet has been increased and conversely after a decrease in diet protein it may be two weeks before the nitrogen excretion is correspondingly decreased I think this fact is probably responsible for misconceptions in the literature based on short term balance studies

When the foregoing conditions are met the nitrogen excretion of the normal individual is equal to his intake and the nitrogen balance is zero On the other hand, if the patient who has a protein deficit is then given an adequate amount of protein his excretion will be less than his intake and his balance is said to be positive Conversely, if a patient shows a consistently positive nitrogen balance it may be assumed that he was previously deficient in protein and is now repairing that deficit Negative balance is simply that state in which excretion exceeds intake It is I think important also to point out that it is not sufficient to measure the nitrogen balance and find it zero in order to state that there is no protein deficit We must give an adequate amount of protein when we measure nitrogen balance The total nitrogen intake as well as the urinary nitrogen and fecal nitrogen were measured daily in patients who were admitted to the hospital with ulcerative colitis The results were surprisingly uniform in all patients studied regardless of the severity of their disease and whether or not they appeared on physical examination to be malnourished

RESULTS OF STUDIES

There is only time to report to you a few of the conclusions which we found to be most interesting In the first place there was evidence of protein deficiency in each of the 5 patients whom we studied definitively and this deficiency existed even in the 3 individuals who were least ill despite the fact that these 3 appeared well nourished with normal serum protein concentrations These 3 individuals had lost little or no weight and had taken a

indicate that lysozyme is an etiologic agent which locally initiates the lesions of chronic ulcerative colitis

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NITROGEN METABOLISM IN PATIENTS WITH CHRONIC ULCERATIVE COLITIS

THOMAS S SAPPINGTON, M D

In the course of the past several years we have been studying the protein requirements of patients suffering from chronic ulcerative colitis at the Graduate Hospital This work was undertaken for several reasons First, because it seemed reasonable to suppose that these patients might be deficient in protein and, therefore, have a protein requirement greater than normal Second, if a protein deficit existed we wished to measure how completely extra protein was used by these individuals, and third, we wanted to measure the loss of protein expressed as nitrogen in the feces Finally, from a practical point of view, this survey would enable us to tell whether or not the patient was getting enough protein in his daily diet in order to meet his needs It was of interest to ascertain whether or not the exhibition of an optimal amount of protein in itself exerts a beneficial effect on a patient who is otherwise maintained on a standard treatment regimen

In the back of our minds was the fact that we know that an adequate amount of protein is necessary for the healing of wounds and for convalescence from infections, etc Therefore, could it be possible that a more or less unrecognized protein deficit could be the cause or at least one of the causes for the tendency of this disease to become chronic with frequent exacerbations?

The problem was approached by means of the nitrogen balance study

erate activity which by barium enema was seen to extend as far as the splenic flexure Laboratory examinations were completely normal except for the presence of blood, pus and mucus in his stools The first nitrogen balance survey was begun a week after admission He consumed an average of 13 gm. of nitrogen per day and excreted an average of 7 gm of nitrogen in the urine and 2 5 gm of nitrogen in his stools, the stool figure was just at the upper limits of normal There was a daily positive balance of 3 5 gm of nitrogen On this regimen he showed steady improvement and the frequency of defecation decreased from four to two times daily His daily nitrogen intake was then increased to 29 gm of nitrogen or approximately 180 gm of protein and the nitrogen balance studies were repeated after sixty days and then again after ninety days The data from these latter studies were similar The daily nitrogen intake was 29 gm and the daily urinary nitrogen had risen to an average level of 18 gm , his fecal nitrogen remained at 2 5 gm daily Therefore positive nitrogen balance averaged 8 5 gm daily, even after high protein feeding for a period of ninety days During this ninety day follow-up period he had been asymptomatic having two formed bowel movements daily I should like to emphasize this patient appeared well nourished even at the height of his illness that his symptoms had never been severe that his weight loss had been but 9 pounds yet a daily protein intake of 180 gm over a period of ninety days had failed to restore completely his protein reserve

INSURING HIGH PROTEIN INTAKE

I should like to say a word about the practical matter of insuring a high protein intake Naturally the mainstay is a well planned attractive diet, high in protein In some places that isn t readily available and it s been found expedient to supplement the ordinary diet with formulas made up of skimmed milk to which is added whole protein in some relatively inexpensive form A suitable formula contains skim milk skim milk powder, carbohydrate and flavoring We have used a mixture of 2000 cc skim milk 120 gm of calcium caseinate and 120 gm of carbohydrate This mixture provides 173 gm of protein and is to be taken daily in connection with the diet

Let us consider the oral use of hydrolysates We are not apt to use them because of their taste, because they are relatively expensive and because they do not seem to be indicated in the ordinary case In these individuals there is apparently no difficulty in protein digestion or absorption If one does use the hydrolysates orally (especially if used in conjunction with tube feeding) it is necessary to avoid using hypertonic solutions A 5 per cent concentration of protein hydrolysate would seem to be a safe maximum If hypertonic solutions are used they are irritating to the bowel and result in the outpouring into the lumen of the bowel of a large quantity of fluid to achieve isotonicity which increases bowel motility and further depletes the patient

SUMMARY

In summary, we don t consider that chronic idiopathic ulcerative colitis is primarily a manifestation of protein deficiency No attempt has been made to

diet containing a minimum of 75 gm of protein and 2500 calories for at least thirty days preceding our study In the second place, all 5 of these individuals were readily placed in positive nitrogen balance by the administration of a moderately large amount of protein either orally or by vein In general, the urinary nitrogen excretion was low, averaging about 7 gm a day That is the picture seen in chronically malnourished individuals This figure was not appreciably elevated when the nitrogen intake was increased as high as 20 gm a day (roughly equivalent to 130 gm of protein daily) This observation seems to conform with the pattern of economical utilization of high protein intake in the chronically malnourished individual After several months of this high protein feeding regimen the urinary excretion gradually rose toward the level of the intake as the deficit was being repaired

In the third place the fecal nitrogen was found to vary considerably In several of the patients it did not exceed the normal level of 2 5 gm of nitrogen per day, in one it was as high as 8 5 gm a day during the period of his greatest diarrhea Fecal nitrogen could not be correlated with the frequency of bowel movements or the severity of the illness in any patient and there was no correlation between the amount of nitrogen given in the diet and the amount excreted in the stools This seemed to confirm our impression that the increased fecal nitrogen in some patients with chronic ulcerative colitis is not due to unabsorbed food, but rather is simply due to the exudate of pus, blood and mucus in their stool

In the fourth place, in each of the 5 patients the attainment of a consistently positive nitrogen balance either preceded or coincided with clinical improvement There was no clinical improvement during any period of negative nitrogen balance We feel that the demonstration of a consistently positive nitrogen balance may enable the physician to predict clinical improvement in the patient critically ill with colitis, or at least to be assured that the metabolic stage is set for such improvement

And finally, the most unexpected finding was the prolonged period during which a high protein diet had to be given these individuals in order ultimately to repair their deficit, even in the case of the least ill patient For example, follow-up nitrogen balance studies on 2 of the patients who had been the least ill indicated that a protein deficiency still existed after a diet consisting of 180 gm of protein and 2500 calories had been consumed for ninety days

I should like to take the time to give you some of the details of the clinical course of one of the patients He was the least sick of any of the patients we studied He was white and twenty-four years of age He stated that a year before entry he had first had symptoms of colitis including diarrhea with blood streaking He was hospitalized elsewhere and had had a complete remission of his disease six months before we saw him At this time his weight was normal Two months before our study he suffered a relapse losing 9 pounds of weight, despite a diet intake of 70 gm of protein and 2500 calories Physical examination on admission showed a well nourished man who did not appear ill and showed no signs of being undernourished

Sigmoidoscopy revealed the typical picture of ulcerative colitis and mod

and the bearing of children Dr Crohn is now well aware that this is no longer true The Koenig Rutzen type of ileostomy bag has made it possible for the average patient to assume fairly normal economic and social activity A number of female patients marry after the establishment of an ileostomy Some have children All seem able to make a satisfactory marital adjustment

The principle of the Koenig-Rutzen bag is quite simple It is fitted and made to the individual measurements of the patient and his ileostomy stoma The bag is sealed to the skin with cement and removed only twice daily, at bedtime and on rising in the morning The sealing of the bag to the abdominal wall prevents leakage and also protects the skin about the ileostomy from the irritation so common to other appliances A small outlet at the bottom of the bag permits it to be emptied into a toilet without removal and without soiling With this appliance an ileostomy is certainly not sufficiently undesirable to warrant delaying surgery when the indications are obvious

COMPLICATIONS REQUIRING IMMEDIATE SURGERY

In the past few years the treatment of complicated ulcerative colitis has undergone a radical change Surgery is safer The blood bank, the medical anesthetist, and the various chemotherapeutic and antibiotic agents permit more extensive operations on more severely ill patients with ever increasing success We have learned that a simple ileostomy offers no assurance that the isolated colon will not obstruct bleed perforate undergo malignant change or act as a serious focus of infection The idea that patients with acute massive hemorrhage and free perforation with peritonitis could not stand surgery has been dispelled Without surgery, the mortality in this group will continue to approach 100 per cent When simple bowel rest through ileostomy does not seem adequate to solve the immediate problem, emergency colectomy is now a reasonable procedure and should be effected without delay

OBSTRUCTION

Obstruction from the acute inflammatory process alone, or later stricture formation may precipitate a proximal perforation For this reason obstruction of even the defunctionalized colon is an indication for prompt surgery The practice of closing the distal ileal stump after ileostomy and dropping it back in the peritoneal cavity is dangerous It should always be exteriorized as a mucous fistula in anticipation of distal obstruction When the obstructive lesion is cicatricial in nature the process is irreversible If such a patient s condition and the surgeon s ability will permit consideration should be given to primary partial colectomy at the time of ileostomy These areas of local cicatricial change are often difficult to differentiate from a carcinoma developing at that point This is an additional reason for considering early colectomy

PERFORATION

In the average patient there are signs and symptoms which suggest an impending perforation These must be regarded as an indication for immedi

compare the therapeutic efficiency of high protein administration with the other generally accepted aids in treatment—chemotherapy, psychotherapy, antibiotics, etc It is probable that all of these measures may be important in bringing about a remission of this disease We wish to emphasize, however, the fact that protein deficiency was found uniformly in these patients and we want to point out that a positive protein balance may be a necessary though doubtless not sufficient condition for clinical remission We would also like to suggest that the period of time for complete restoration of tissue protein may be very lengthy and that a partially corrected unrecognized chronic protein deficiency may be a very important factor in bringing about relapse of the disease

SURGERY OF THE COMPLICATIONS OF ULCERATIVE COLITIS

LLOYD W STEVENS, M D

This is a consideration of the complications of chronic continuous and chronic relapsing ulcerative colitis To us these are difficult problems The course of the disease even after fecal diversion by short circuiting operations or ileostomy is unpredictable and often explosive Postoperative difficulties are frequent and require endless hours of care and attention We are, therefore, delighted when the skill and perseverance of the gastroenterologist combine to arrest progression and render the patient economically and socially fit In a considerable group, however, complications develop and surgical intervention is imperative Many misconceptions still exist with regard to this surgery *I wish to consider these in the light of recent experience*

SURGERY—THE MORTALITY AND HANDICAP IT IMPOSES

Delay in surgical intervention has frequently been justified on the basis of an expected high mortality In clinics, with considerable experience in the surgical management of these complications, the mortality of ileostomy now ranges between 3 and 5 per cent, the mortality of colectomy is considerably less During the past two years we have had no deaths in over 60 consecutive major procedures performed for these complications Recent advances in anesthesiology, the use of antibiotics and chemotherapy, the availability of large quantities of blood at a moment s notice and an increasing understanding between gastroenterologist and surgeon, are largely responsible for this dramatic improvement in operative risk

A second reason commonly given for delaying necessary surgery is the feeling that an ileostomy dooms the individual to a life of seclusion and restricted activity Dr Burrill Crohn once said that for the young woman "an ileostomy is a complete frustration and denial of all romance, marriage,

changes Perforation is often masked and the diagnosis made difficult because of the frequency of fever, abdominal tenderness pain and muscle guarding in the course of non perforating disease (3) There is a close relationship between hemorrhage and perforation Both indicate deep destruction of the bowel wall (4) Emergency colectomy for exsanguinating hemorrhage and perforation with peritonitis was successfully carried out in a critically ill patient Without it the patient would undoubtedly have died

Case 2 B S male forty six years of age He was hospitalized on 10/4/47 with a two year history of chronic relapsing ulcerative colitis At the time of admission he was acutely ill anemic and bleeding He was placed on an intensive medical regimen from 10/4/47 to 11/6/47 Despite this his course was progressively downhill He had repeated massive hemorrhages and episodes of shock At times he passed clots of blood per rectum that looked like casts of his bowel He had many emergency transfusions his condition was desperate at all times On 11/8/47 he developed a perforation of the proximal colon with spreading peritonitis apparently secondary to an acute inflammatory obstruction at the splenic flexure An emergency ileostomy was carried out and the perforation sealed Despite this he rapidly grew worse From 11/21/47 to 11/24/47 he had hemorrhages from the bowel which measured from 500 to 1000 cc daily On 11/24/47 an emergency colectomy was carried out for uncontrolled bleeding The colon was removed from the distal mucous fistula of the ileum down to the sigmoid He made a relatively uneventful though prolonged recovery The required blood replacement during hospitalization was 21 000 cc of whole blood 4000 cc of plasma and 6000 cc of the plasma equivalent of concentrated serum albumin Surely no one can question the fact that all conservative measures had been exhausted in this instance

This case illustrates (1) Obstruction of the colon occurring during the acute stage of the disease from edema and angulation There was no actual cicatrix at the site of obstruction in the splenic flexure (2) Obstruction as a factor in proximal perforation of the colon (3) The fact that ileostomy does not always prevent further complications in the defunctionalized colon (4) The close relationship between massive hemorrhage and perforation (5) The favorable outcome of emergency surgery and treatment in a patient dying from profuse uncontrolled hemorrhage in which every conservative adjunct had been exhausted If patients such as these can survive emergency colectomy, surgery should no longer be so formidable for the average complications of ulcerative colitis These are examples of what concerted surgical effort has to offer these desperately ill patients today

COMPLICATIONS REQUIRING ELECTIVE SURGERY

1 Polyposis
2 Granuloma formation
3 Neoplasm
4 Fistulas and sinuses
5 Intractable secondary complications such as arthritis, iritis and dermatitis

These are the complications that we believe require prompt elective surgery The gravity of the problem in the first three of these complications I do not

ate surgery At times the diagnosis is difficult since the association of fever, leukocytosis, abdominal pain and tenderness is so common in acute, non perforating disease However, when the clinical picture changes, one should suspect a change in the underlying pathology These perforations, like other complications, may occur in the isolated as well as the functioning colon The importance of distal obstruction as an etiologic agent has already been stressed An equally important point in the etiology of perforation is ill advised handling of the bowel at the time of the original ileostomy The average colon of an ulcerative colitis patient requiring ileostomy will not tolerate very much handling For this reason, palpatory exploration of the colon is to be avoided at the time of ileostomy

UNCONTROLLED BLEEDING

This complication is fortunately rare The idea has been proposed that bleeding in ulcerative colitis can be controlled on a medical program alone This is usually true Uncontrolled bleeding, for this reason, has not generally been accepted as an indication for surgery As in the active bleeding from peptic ulcer, this is, of course, the most undesirable time to operate upon these patients I am equally certain that some will die of hemorrhage if not operated upon When massive bleeding occurs during the course of adequate medical treatment, and continuous blood replacement can barely keep up with blood loss, more definitive treatment must be employed Nothing short of a subtotal colectomy will suffice

Two recent experiences with emergency problems of this type will serve to illustrate certain of these points

Case 1 R. G female thirty years of age was admitted to the Graduate Hospital of the University of Pennsylvania on 10/8/47 with a history of chronic recurring ulcerative colitis of four and one half years duration She was treated in the hospital on an intensive medical program until 1/24/48 Because the disease was progressive under this intensive medical treatment an elective ileostomy was performed on 1/24/48 The patient did well until 1/31/48 when there was an abrupt change in the clinical picture with the onset of fever back pain abdominal pain and a high leukocytosis This continued until 2/10/48 when repeated massive hemorrhages from the rectum and from the mucous fistula of the distal ileum appeared During a forty eight hour period the measured blood loss from the colon was over 4000 cc The patient was in and out of shock on a number of occasions On 2/13/48 there was an abrupt change in the clinical picture The bleeding from the rectum and mucous fistula stopped Signs of spreading peritonitis were apparent The patient appeared in desperate condition with a distended rigid abdomen and the facies of peritonitis As a measure of desperation an emergency colectomy (from the terminal ileum to the mid sigmoid) was carried out on 2/14/48 Four liters of blood and pus was aspirated from the peritoneal cavity There was a free perforation of the cecum Peritonitis was generalized This patient recovered

This patient illustrates certain significant points (1) Ileostomy does not always prevent progression of the disease, in this case perforation and massive hemorrhage appeared shortly after the colon was defunctionalized (2) When the clinical picture in ulcerative colitis changes, the local pathology

RELATION OF THE VAGUS NERVE TO THE INTESTINES

In the first place, from an anatomic point of view, it is believed that the vagus is the nerve, the parasympathetic nerve, which is concerned with motor and secretory function of the small intestine and of the colon as far as the mid transverse portion, whereas the parasympathetic outflow from the sacral autonomic fibers is supposed to supply the distal transverse colon and the remaining large intestine This anatomic knowledge is based first on embryologic development, and secondly on various experimental studies Schmidt in 1933 sectioned the vagus nerve in one group of animals and the sacral autonomics in another He used both dogs and cats and stained the preparations with silver chloride in order to demonstrate what degeneration took place in the bowel wall The normal large intestine shows longitudinal nerve fiber bundles in the serous layer which increase in size and number toward the distal end of the colon In the group of animals in which the vagus was sectioned just below the diaphragm there was a degeneration of nerve fibers in the ascending and transverse colon, with no degeneration in the descending colon In the group in which the sacral nerves were divided, there was degeneration throughout the colon but the changes were less marked in the ascending and transverse colon In this group the fibers of the myenteric plexus were also degenerated

These findings are almost all we know concerning the anatomy of the vagus nerve or of the parasympathetic nerves and their supply to the colon From a physiologic and perhaps pharmacologic point of view we are also not very well informed In 1938 White and Jones demonstrated that pilocarpine, a parasympathetic stimulant, produced changes similar to those of colitis when applied to the mucosa of the colon Physostigmine, an inhibitor of cholesterinase, produced the same effect though requiring longer for its action With barium enemas during the administration of these drugs increased haustration, areas of spasm and increased motility were shown The authors stated that stimulation of the sacral divisions of the parasympathetic nerves should also produce mucosal changes in the bowel Conversely it might be expected that division of these nerves might prevent these mucosal changes

From a physiologic point of view the action of the parasympathetics either vagus or sacral outflow, is not too well known Back in the days of Pavlov the vagus was sectioned and Dr Thomas, who reviewed this subject very carefully in a recent number of Gastroenterology stated that in the cases with vagus division there was a definite change in the irritability of the bowel which appeared to be a hyperirritability of the colon and small intestine These experiments have been repeated and it is believed that the changes after complete vagotomy are hypomotility of the stomach, hyposecretion of the stomach and pancreas and possibly the intestine, together with a peculiar hyperirritability of the intestine These changes are interpreted as being mainly due to a loss of the tonic activity of the abdominal vagus The knowledge that we have concerning parasympathetic activity in the colon and small gut is certainly relatively meager

believe is generally appreciated The abnormal epithelium which lines the colon, whether it be polypoid in character or not, is extremely prone to undergo malignant change At the Lahey Clinic, for example, malignancy was found in 7 per cent of all the colons treated for ulcerative colitis Furthermore, of the patients who had the disease for nine years or more, 1 in 3 developed carcinoma in the colon This type of carcinoma we know is highly malignant and often multiple

Any colon which shows polyposis or irreversible mucosal change over a period of time should be removed promptly Furthermore, any inflammatory *mass or so-called granuloma associated with the colon of ulcerative colitis* should likewise be removed, since in our experience it is impossible to distinguish such a lesion from carcinoma by gross examination Colectomy *should never be delayed for long periods of time in the presence of these* complications Finally, any colon defunctionalized by ileostomy should be observed periodically If no indication for colectomy exists, barium enemas and sigmoidoscopic studies should be made from time to time to early detect evidence of complications Only in this way can the threat of this rapidly metastasizing tumor be removed

RATIONALE OF VAGOTOMY IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

L KRAEER FERGUSON, M D

What I m going to say is in the realm of speculation It is speculation, however, in which probably all of you have joined, because we are in an uncertain situation with regard to ulcerative colitis and regional enteritis We know that what we do is in the nature of care of the end stages, the complicating stages of the diseases We have speculated as to how we might be able to treat these diseases in an earlier stage, when they may be amenable to less destructive treatment, and this thought and these *speculations have* been shared by the surgeon and the gastroenterologist

The question of the relation of the vagus nerve to the gut is an old one which has been recently revived, first by the wave of enthusiasm for vagotomy in treatment of ulcer, and secondly by a group of workers at the University of Minnesota, especially Dennis, who has written concerning the use of vagotomy *in the treatment* of regional enteritis and ulcerative colitis

Before we go into a review of his work, which is all that I am going to attempt this morning I would like to mention a few of the facts that are known concerning the vagus and the gut, and these are very few and somewhat nebulous perhaps in many respects

a definite history of urgency to defecate on partaking of food had relief from this annoying difficulty following vagotomy

Now I don't believe that these observations prove anything definite but they do open up a field for speculation in cases in which we are apparently helpless otherwise You heard Dr Thomas say that he didn t think the vagus had any effect upon the intestine or colon which was normally acting but these intestines and colons are not normally acting The question arises as to whether or not vagotomy may be a method of therapy worth while considering

PANEL DISCUSSION

Question I would appreciate more information on the new antilysozyme, sodium hexadecyl sulfate Is it available commercially and how long does therapy require?

Dr Prudden It is not available commercially We obtain a crude preparation containing a considerable amount of alkyl alcohols and sodium sulfate from du Pont and recrystallize the sodium hexadecyl sulfate by extraction with ether and alcohol from the crude mixture If the compound continues to give encouraging results, some arrangement for wider distribution will doubtless be made

Nisulfazole is obtainable commercially It is manufactured by the George A Breon Company of Kansas City It is limited by the Food and Drug Administration to investigational purposes, and doctors employing it are asked to report their results

The time element has been quite variable Two of the patients have gone into remission promptly within five days Other patients have been kept on the drug from four to five weeks before the lysozyme titer fell and the stools began to solidify We have no explanation for this difference although it appears to be related in a rough way to the pre treatment lysozyme titer

Question Have you noted any ill effects from sodium hexadecyl sulfate?

Dr Prudden There has been no apparent systemic toxicity Liver function tests, blood urea nitrogen blood counts, urine analyses etc , have all remained normal Some have, in fact improved with treatment of the colitis Because it is a large molecule, there is an osmotic effect and one may get a watery diarrhea This tends to improve in proportion to the improvement in the colitis

Question Have you used this therapy in ileitis?

Dr Prudden Yes, we have in 2 patients The 2 patients have definitely improved and are now feeling a great deal better The lysozyme titer is not a reliable index of the activity in enteritis because the drug increases the rate of fecal expulsion Therefore the amount of lysozyme inactivation is decreased For this reason the titers in treatment have remained the same or

RESULTS OF VAGOTOMY

Dennis, working at the University of Minnesota, was faced with a problem presented by the Medical Chief, Dr Watson This was a patient in whom the colon and five-sixths of the small intestine had been removed The patient continued to have diarrhea and rapidly went down hill Dr Watson suggested to Dr Dennis that if possible it might be worth while to divide the vagus in an attempt to slow down intestinal transport In this case he did the vagotomy above the diaphragm with striking improvement in weight and the passage of normal stools, the improvement was temporary The patient later had to have a revision of the ileostomy, but is still living, relatively well

This initial experiment stimulated interest in the question of vagotomy in the treatment of ulcerative colitis and in regional enteritis In a recent publication Dennis reported 28 cases of vagotomy, 25 of these had been followed for a significant period and in 16 of the 25 vagotomy was the only surgical procedure Of the 16 treated by vagotomy alone, 6 had become asymptomatic, 4 improved, 5 are not improved and 1 is worse Of the 5 listed as not improved, 1 had amebic dysentery, 1 has had a reduction in the number of stools from 18 to 9, but refused further treatment, 2 were well for many months only to suffer a recurrence of diarrhea, and 1 was well for three months and then suffered an acute exacerbation, requiring emergency ileostomy

In other words, his cases have not been 100 per cent improved, nor does he claim any such results Despite the equivocal results, in general there has been an average weight gain of 15 per cent An evaluation of proctoscopic changes revealed 4 cases in which an actively diseased mucosa had assumed a normal appearance In 7 there was definite improvement without complete healing

Dennis was interested in this problem and studied these cases in various ways First he was interested in knowing whether or not the vagus section did slow down intestinal transport It was found that the transport preoperatively was approximately three hours from pylorus to colon, whereas postoperatively it was seven and three tenth hours He was only able to carry out such studies in one or two cases He found that the difference in colon transport was increased from three and a half hours to eleven hours These figures may be significant in considering methods of slowing down intestinal transport

Furthermore, he studied some of these patients before and after vagotomy by stimulating them emotionally Emotion has been shown to produce definite changes in the colon In the 2 patients who were studied before and after operation, there was a definite hyperemia of the rectum as seen by proctoscopic examination when sore topics were discussed with them, whereas postoperatively this hyperemia was absent

He was also able to study some patients in a similar way who had a vagotomy performed for duodenal ulcer He noted the definite blushing of the mucosa with increased secretion when these patients were irritated, where a blanching or no change followed vagotomy Furthermore, 2 patients who had

Dr Stevens That is correct The pathologic process is not that of adeno matous polyp it is merely areas of isolated hyperplastic mucous membrane which remain between areas of scarring That however, does not change its malignant potential

Question What is meant by minimum polyposis which renders colectomy advisable?

Dr Stevens The tendency today is to remove all these colons after ileostomy if the process is believed to be irreversible so that any polyposis which was present would probably, in our minds constitute an indication for colectomy

Question Comment on the immediate postoperative care of ileostomy

Dr Stevens These patients, after ileostomy leave the operating room with a soft catheter in the ileum which is drained into a bottle The immediate difficulties that we run into in the postoperative care are matters of fluid balance These patients often will lose tremendous amounts of electrolyte through the ileostomy and one has to be constantly on guard for that following the patient from the point of view of serum chlorides and other measures of fluid balance After the tube is removed on about the fifth postoperative day, the problem is even more acute because one does not have a measure of the amount of the ileal drainage The skin about the ileostomy opening becomes a problem after removal of the tube, we attempt to solve it by painting the skin with a thick coating of aluminum paste 10 per cent powdered aluminum and zinc oxide ointment The other medical measures which have been in progress prior to ileostomy are continued

Question How do you feel about ileostomy in uncomplicated ulcerative colitis with the idea of diverting the fecal stream resting the colon and re anastomosing in one or two years

Dr Stevens We have had practically no experience with this The patients that we see with ulcerative colitis have been followed by gastroenterologists and the decision for operation usually comes in consultation with them We would be interested in this I might add however, that the experience with reanastomosis of the ileum after a period of time has been distinctly disappointing I know of only two patients that have had a successful reanastomosis in our experience, and at the Lahey Clinic for example, where the surgical experience with ulcerative colitis is extremely extensive they have had only a handful of successful reanastomoses

decreased only very slightly Since we have used the lysozyme titer as the index of improvement and as the indication of when to stop therapy, it has been difficult to assay the results objectively

Question Does mucin have any antilysozyme effect?

DR PRUDDEN We haven't tested commercial mucin I would doubt very much that it does

Question In terms of the lysozyme theory, how do you account for the remissions in ulcerative colitis?

DR PRUDDEN It is believed that the colonic lysozyme titer falls, the mucosal lesions are covered with surface mucus, and the ulcerations heal under this protection The mechanism of intestinal lysozyme production is not yet understood Data which we will report soon appear to indicate that autonomic imbalance, per se, is not responsible

DR BOCKUS Does the lysozyme titer increase prior to a recurrence?

DR PRUDDEN Yes, I think we can say that it does On several occasions we've proctoscoped individuals that have been in remission and noted a normal mucosa There has then been a rise in the lysozyme titer and the mucosa over a very short period of time has become very red and friable without visible ulcerations This has been followed by the onset of symptoms, and finally of rectosigmoid ulcerations visible at proctoscopy

Question Does skim milk powder, in your experience, aggravate colonic irritability in ulcerative colitis?

DR SAPPINGTON I would answer that by saying that in my experience it does not, but I am sure there are causes when it may I imagine the interrogator is thinking in terms of the irritability of the colon which may be due to the ingestion of milk Fortunately we have not run into that with the exception of one individual who said that all of his life, as far back as he could recall, milk had aggravated a tendency toward diarrhea Therefore, in making up his formula, we used water rather than skim milk but the skim milk powder was employed and in that instance did not aggravate, as far as we could tell, his diarrhea due to the colitis

Question Do you explore the abdomen—i e, inspect the colon—at the time of ileostomy?

DR STEVENS The answer is that routinely we do not We inspect what colon we can see through a small muscle splitting incision in the right lower quadrant We do not handle the colon unless at that particular time there is some indication for going ahead and doing a colectomy, as in the case that I mentioned before, the patient who had two masses in the bowel that were thought to be malignant The experience with handling of the colon and doing exploratory procedure is particularly bad because these colons do not stand handling, they often will break down and produce a perforation

Question Is not the lesion in the mucosa of the colon a pseudo-polyposis rather than polyps or polyposis?

Carcinoma of the Colon

SIGMOIDOSCOPY IN THE DIFFERENTIAL DIAGNOSIS OF RECTAL BLEEDING

JOHANNES F PESSEL, M D

We should like to designate 'rectal bleeding as the number one cause of anxiety states in gastroenterologic patients This we believe to be the result of recent lay literature and advertisements by various groups, which have tended to impress patients with the fact that a small bit of blood expressed from the rectum is a sign of carcinoma The anxiety state is first expressed by the patient because the information may be correct secondly, by the physician because the patient s fears may be justified or, if not they may be difficult to dispel Furthermore to find the true source of bleeding may be a most arduous task

It is our belief that at times bleeding from the rectum is much more difficult to explain than is upper gastrointestinal tract hemorrhage Vomited blood can come only from the stomach or the esophagus but blood found in the stools particularly on chemical examination may come from anywhere in the tract Blood found in the rectum therefore can result from bleeding in a far greater area and from a far more variable source

The causes of rectal bleeding are indeed extremely important because blood in or around the stool may, unfortunately mean carcinoma The incidence of adenocarcinoma of the lower bowel is very high and the time lost prior to operation is still too long This delay according to Leach, is no longer due in a large measure to the patient but is the result of indecision carelessness and an unnecessarily laissez faire attitude on the part of physicians Rankin makes the statement that bright to dark red blood mixed with the stool appearing with the passage of mucus associated with obstipation is the cardinal sign of malignant involvement of the distal segment of the colon Positive tests for occult blood may result from bleeding anywhere from the buccal cavity to the anus Red blood, persistently in or on the stool in a majority of instances indicates a lesion in the colon distal to the splenic flexure Lesions of the right colon usually present blood of a dark color In 539 cases of carcinoma of the rectum, Rankin found that bleeding was the outstanding symptom for a period of several months and noted that there was blood in the stool in 89 5 per cent of the cases Buie reports 80 per cent of cases of rectal cancer with positive occult blood in the stools Rosser reports 78 per cent Browne states that in his series of rectal carcinomas bleeding was a universal predominant symptom

standing the patient on his feet and increasing the intravascular tension may produce serious spurting of a small arteriole Some years ago, one of our clinic patients returned in the late afternoon requiring three transfusions as a result of such a severe hemorrhage

Rectovaginal fistulas, vesicovaginal fistulas secondary to neoplastic diseases of the vagina, cervix, uterus or bladder may produce serious rectal bleeding Draining appendiceal abscesses have been known to be the cause of sanguineous mucopus in the rectum Ruptured pelvic abscesses into the rectosigmoid have occurred within the experience of all of you These too, may be associated with considerable bleeding This does not cover all of the possibilities

USE OF THE SIGMOIDOSCOPE

It is because of the multiplicity of the reasons for rectal bleeding that every method available must be used in an attempt to obtain an explanation and a diagnosis Hence, the efforts of the physician toward inspection and intubation were a natural result What we can visualize, we can understand and in most instances diagnose Our medical grandfathers inspected the tongue looked down the throat and eventually attempted to look into the rectum This resulted in the appearance of the anoscope which grew into an 8 inch sigmoidoscope The 8 inch sigmoidoscope developed into the 10 inch instrument and recently, into a 16 and even a 20 inch tube

It is our feeling that an examination of the rectosigmoid with the finger the anoscope and a sigmoidoscope should be part of the routine of everyone interested in gastroenterology It is a simple procedure and should not be attended by accident, providing of course that due care is exercised You should run into no difficulties if you will make it a hard and fast rule never to introduce the sigmoidoscope into a rectum that you have not recently examined and lubricated with the index finger Furthermore, never insert the scope blindly, but only under direct visualization See the lumen before advancing the tube At the Graduate Hospital where we have had many student physicians examining thousands of patients, we have, to date, had no disturbing results We believe sigmoidoscopy to be a safe procedure in the hands of a careful examiner

Direct visualization often leads to a definitive diagnosis At times swabs cultures and biopsies may be required Sigmoidoscopy at times proves to be a preventive measure because polypi, which are found and removed may save the patient a malignancy later on

Sigmoidoscopy permits of visualization of from 1 to 20 inches of the lower colon True enough, the longer instrument in our experience at the clinic is seldom used, but it proves most helpful in a particular case where mucopus or blood is trickling down from an area above the 10 inch level In these rare instances a longer scope often aids in arriving at a diagnosis The instrument you are most accustomed to is, perhaps, the best I was taught to use the Lyon Bartel instrument and another may prove clumsy in my hands The instrument that you were trained with and that you have had the most experi

CAUSES OF RECTAL BLEEDING

Let us review the possible causes of rectal bleeding These are more numerous than the letters in the alphabet To enumerate some of these one may mention diverticulosis, proctosigmoiditis (acute, chronic or factitial), intestinal obstruction due to volvulus, hernia, intussusception, lymphogranuloma venereum, acute enteritis, ulcerative colitis, acute or chronic bacillary dysentery, amebic dysentery, tuberculous colitis, regional ileitis, infection of the colon by fluke, and direct injury of the rectum Injury of the rectosigmoid is commonly overlooked by many of us The swallowing of the breast plate of a chicken, a terrapin shell, a piece of oyster shell, the claw of the crab or lobster, or even a small portion of glass is an all too common occurrence, particularly among those who eat too rapidly For some reason, often these bits of material may do no harm until they reach the rectum, where they may become imbedded in the mucous membrane and produce acute injury or even ulceration almost invariably associated with bleeding and often a great deal of pain

To go on with other causes of bleeding, we must mention single polyp as well as multiple polyposis or degenerative polypi secondary to an ulcerative colitis, uremic colitis, typhoid or paratyphoid ulcerations of the bowel, congenital hemangiomas and blood dyscrasias Purpura haemorrhagica, due to various causes, has been known at times to produce blood in the stool Frequent causes include hemorrhoids, fissures, fistulas, cryptitis, and, finally, even severely irritated pruritus ani Duodenal ulcer may cause the passage of cherry-colored blood in the feces because of a marked hypermotility of the intestine Serious infectious diseases of various and sundry sorts may occasionally produce blood on or in the stool

Occasionally a patient will appear with the story that he has passed blood only to find that he has ingested a large quantity of beets When questioned, he will admit that the blood in the toilet bowl was more purplish red than red, more beet color than blood color A careful discussion of his previous twenty-four hour diet will enlighten you as to the cause At moments, bits of tomatoes, pimientos and other red substances, which have been ingested the day before, will simulate blood

We cannot take time to discuss the exanthemas and diseases of infancy Mercurials taken by mouth will produce violent mucosanguineous discharges I recall one woman, who injected four 7½ grain tablets of bichloride of mercury dissolved in 1 quart of water into the rectum by accident because the douche bag had been prepared for other purposes and had not been emptied before the enema was taken The result was a disastrous chemical colitis with severe hemorrhage

At times patients fail to advise you that they have had a recent biopsy by Doctor 'X' down the street the day before Vigorous sigmoidoscopy or biopsy of a polyp may produce excessive bleeding, almost exsanguination, particularly when you use an inverted position during the process of obtaining these biopsies Although bleeding may not occur in the inverted position,

roentgen diagnosis of cancer of the colon and to evaluate errors in diagnosis as a frequent effect of inadequate attention to technical details

A thorough and satisfactory x ray examination of the gastrointestinal tract is of tremendous diagnostic value and importance, not only in proportion to the quality and detail of the x ray films, but also in relation to the meticulous routine methods of demonstrating these defects in a series of x-ray films made with many varying angles and with varying degrees of compression and in conjunction with supporting fluoroscopic observations

The detection and demonstration of early cancer of the colon generally requires special efforts and skill as well as more than the usual extent of combined fluoroscopy and numbers of x ray films that are ordinarily employed in a routine roentgenologic survey study of the colon A suspicious history therefore demands additional studies beyond the ordinary amount of detail that a routine gastrointestinal study, in the absence of colon symptoms, would entail

CONDITIONS LEADING TO TECHNICAL DIFFICULTIES

While it is true that there are problems and difficulties in the x ray diagnosis of disease of the colon it is likewise true that these problems are very generally the result of some technical deficiency or inefficiency Some of the problems involving faulty technical procedures are commonly related to the following circumstances

A very sick patient may be too weak to tolerate the physical strain of rotation and manipulation that an opaque enema study routinely involves A plain or scout film survey may be the only x ray study that can be done Such an examination may show abnormalities i e soft tissue masses calcifications bone disease, but also may confirm or strongly suggest early effects of perforation or obstruction

An uncooperative patient is not always an insurmountable problem Patience and perseverance will overcome most of the obstacles that are encountered with the mentally and physically sick individuals An unsatisfactory barium enema study may be ascribed to an uncooperative patient when the circumstances of a poor technical result are actually an effect of a very tired or a very impatient and irritable examiner

Inability to retain the enema under fluoroscopic guidance may be due to many factors which can largely be controlled Specially inflated rubber-collared enema tubes will satisfactorily control regurgitation resulting from sphincteric relaxation or damage Frequently, mild sedation may be necessary and sometimes even morphine may be required to control pain and discomfort from a barium enema procedure

If the introduction of the enema is carried out slowly the distress is frequently mitigated Rapid filling is usually associated with deep-cutting circular spasms and distress in the irritable type of colon The resulting spontaneous filling and emptying of wide segments of the colon and the writhing effects of to and fro movements are quite typical of the irritable bowel and are usually associated with marked and sometimes uncontrollable discomfort

ence with is the instrument of choice for you The more you use it, the safer you feel with it, the greater are the possibilities of doing your patient a service Use it often enough so that you feel comfortable with it

Most of us think that a definite diagnosis of a simple polyp or a carcinoma can be made by visualization With experience, you will be able to differentiate between an ulcerative colitis and an amebic infestation You may not always be able to differentiate between a tuberculous and an amebic ulcer, but after a great deal of experience, you may do even this

As time goes on, it is quite within the realm of possibility that more diseases will be studied through the sigmoidoscope, particularly the acute exanthemas, as more men become interested and avail themselves of this helpful diagnostic procedure If you do not find an answer on your first examination, try again A polyp seen last week may not be found this time, although you have it recorded in your records Conversely, one that you have not found this week you may find next Occasionally too vigorous preparation with too hot or too alkaline a soapy enema may give you a false impression Hence, examination with and without preparation may be important and may actually lead to a satisfactory diagnosis

You realize that the sigmoidoscope visualizes, shall we say, the lower 20 inches of the rectosigmoid and that some of this is difficult to demonstrate by our friends, the roentgenologists Most of us have had this experience namely, that a polyp visualized or seriously suspected in the rectosigmoid because of symptoms and persistent blood in the stool could not be demonstrated by x-ray Fortunately, most x-ray investigators will advise you to repeat the x-ray examination or will do it automatically when the first examination fails to show a lesion We have dozens of instances in which the lesion was not found the first, the second or even the third time by roentgenologic examination, and yet it was beautifully portrayed in the fourth examination In one instance, it was a benign polyp In another, it was a sessile malignant adenocarcinoma The bones of the pelvis, the obesity of patients in middle life, when malignant diseases of the rectosigmoid are most wont to occur, make x ray examination and the rectum and rectosigmoid only partially reliable Hence, endoscopy of the rectosigmoid is of prime importance

PITFALLS IN THE ROENTGEN DIAGNOSIS OF COLONIC MALIGNANCY

BERNARD PIERRE WIDMANN, M D

This discussion is not intended to be a discourse on the roentgen signs of disease of the colon Its purpose is to discuss some of the pitfalls in the

laboratory—in the hospital as well as private office Negative fluoroscopic impressions are not always substantiated by multiple x ray films made at varying angles and with varying degrees of ' filling and varying degrees of compression Such a conflict must be confirmed or ruled out by reexamination Conversely, apparent negative x ray films may belie abnormal fluoroscopic findings—especially in cases of reduplication and redundancy

Borderline defects may be an effect of simple spasm of a neurogenic character or spasm in relation to a benign, shallow ulcer, a sigmoiditis or diverticulitis, but the possibility of early carcinoma must also be entertained and disproved by repeated x ray examinations Polypoid defects as a rule, are not simply and clearly demonstrated by a single examination

Defects of organic disease are often simulated by gas and fecal masses Incomplete filling pressure of spine and extra colonic masses require additional examinations Overdistention or a complete filling of the colon with a barium enema may mask or obscure a small non-obstructing lesion There are frequent situations that require additional x ray studies when the question of a carcinoma of the colon is clinically suspected

X PAY METHODS OF EXAMINATION OF THE COLON

1 The barium meal or progress meal study
2 Barium enema
3 Post evacuation film
4 Contrast air study

1 Barium meal studies of the colon are not done when the question of a colon lesion is clinically suspected If however the colon study is considered as part of a routine gastrointestinal examination, then the colon outline as shown by concomitant x rays and fluoroscopy made at varying intervals of a half to one hour after a barium water meal may give excellent information as to variations in tone, mobility and outline of the mucosal pattern (Figs 242 and 243) Defects of organic disease may not be definite but can then be controlled by barium enema If there is a suspicion of an obstructing process then barium meal should never be given A plain or scout film should be done An opaque enema study can safely follow this preliminary investigation

The study of function and the status of postural tonus are often more satisfactorily revealed by progress meal observation then by the barium enema alone In many instances, the terminal ileum may be visualized more clearly by progress meal studies This should be a supplementary procedure to the enema when there is a clinical suspicion of disease in the ileocecal region and more particularly if the opaque enema fails to regurgitate into the terminal ileum In the majority of instances, the opaque enema study, if carried out slowly and with gentle manipulation and rotation will result in sufficient regurgitation of barium to portray the caliber wall flexibility and mobility of the terminal ileal segment and particularly to show an excellent outline of the anatomic contour of the ileocecal juncture

2 *The barium enema* or so called opaque enema study is an indispensable

Anxiety and fear as to what might be found, or the memory of a previous unsatisfactory and distressing examination, calls for judgment and patience and some psychologic uplift on the part of the radiologist Transient zonal spasm must be noted for subsequent comparison

An obstructing spasm with opaque enema is usually associated with uncontrollable pain and regurgitation The result may be doubtful and the condition must be checked and double-checked as a possible effect of carcinoma If the site of the spasm is beyond the reach of the sigmoidoscope and obstruction persists even after several additional examinations and in conjunction with sedation, the possibility of carcinoma must then be considered until proven otherwise

Too much haste on the part of the examiner is a very common fault in many radiologic departments—both private and hospital laboratories The stress of heavy schedules and the desire of the radiologist to comply with special requests for additional or emergency work may precipitate confusion and even carelessness and may result in an "oversight" of serious importance

Too much haste and methods of "short-cuts' eventually result in a poor quality of film movement, breathing, developmental artefacts, scratches, stains and improper development as to time and temperature These are academic criticisms, but the quality of the work reflects the skill and training not only of the departmental personnel but also of its director These are influences that undoubtedly precipitate many erroneous interpretations

A lazy or indifferent operator reflects his attitude as well as his ability in the services of a dependent technician Such a radiologist will not produce the best type of work *This is inefficiency and is a discredit to a specialty that* offers such tremendous advantages and possibilities of diagnostic benefit It is only natural that this attitude must eventually result in a loss of confidence and respect of his colleagues

The radiologist may not always allow sufficient time for proper accommodation of his eyes This is a handicap to good fluoroscopy

The x ray department is an expensive division of the hospital The high cost of equipment and replacement, the supplies and the large secretarial and technical staffs necessary for the efficient performance of the duties of a large department, require the budgeting skill of an expert administrator Even though this is very true and most important, it is outright false economy to budget the number of x-ray *films to be used for examinations of any particular* anatomic region

A colon study may require prone, supine, right and left oblique as well as erect posture views to unfold and isolate reduplicating loops of the barium-filled bowel Similar views may be necessary to show the mucosal pattern of the colon in the ' post evacuation ' films These additional films and angles may also be necessary for contrast air studies and in conjunction with spot and compression films, particularly for cases of intermittent or persistent bleeding or for patients presenting questionable clinical, physical and roentgen findings

A rule to check' and ' double-check should be the motto of every x ray

would experience with an ordinary, small cleansing enema, that the purpose of the examination is to fill the bowel with an opaque solution which, in turn will permit the taking of an x ray 'picture, that the only difference between the opaque enema study and a simple cleansing enema will be the advantage and necessity of watching the bowel fill, inch by inch, as the head of the barium column passes along from the rectum and on around from the left to the right side, and when all parts of the bowel have been seen to fill completely, a picture will be flashed quickly and the patient can then go into the bathroom and finally, that the entire procedure will take a few minutes



Fig 244 Dual carcinomas—ascending and transverse colon This illustrates the occasional advantage of complete filling of the colon but there is risk of precipitating obstruction when a narrow napkin ring deformity is shown

Such an explanation eliminates fear and anxiety and helps to build up the confidence of the patient and develops a better state of relaxation and co-operation

Fluoroscopically with rotation, palpation and compression it is possible to determine the most suitable angles for radiography The radiologist should aim to portray in the x ray film the normal and abnormal appearances seen fluoroscopically This information not only enables the referring physician to check and compare the word description of the report and the interpretation but it also serves as a valuable record for future comparison for consultation and possible difference of opinion

An incompletely obstructing carcinoma of the colon may be obscured by

and important procedure In order to obtain an outline of the colon, it is necessary that all parts be visualized under conditions of abnormal intra colonic tension The enema study permits a gradual filling and a satisfactory



Fig 242 Failure to demonstrate ileocecal regurgitation into terminal ileum at time of the opaque enema study (A) necessitates further observations in a progress meal study in (B) this is shown to be an effect of a regional ileitis



Fig 243 Progress meal studies may show significant abnormalities (A) and (B) are variable outlines of the same patient at monthly intervals and showing changes in degree of a lymphosarcoma with terminal ileal involvement

observation under circumstances of varying degrees of filling The technical results are enhanced if the radiologist discusses with the patient the details of the examination and the procedures that are involved The patient should accordingly be told 'That the examination is nothing more than what he

It should be emphasized that partial or complete obstruction to a retrograde introduction of barium water enema is a strong sign of a probable neoplastic process Furthermore, obstruction to the flow of an enema is not always related to obstruction of the normal transit of the bowel content

There is always a question as to how much barium should be introduced beyond the fluoroscopic evidence of an obstructing process There is a possibility that there may be spasm and resulting retention of barium beyond the site of the disease Barium impaction may precipitate obstruction (Fig 244) On general principles, it is well to discontinue the enema procedure if the fluoroscopic evidence of carcinoma and its character and extent of involvement are clearly outlined and a good film record of the defect has been obtained There is only a small chance that there may be a second lesion in



Fig 246 Multiple defects due to incomplete filling and so called dirty bowel gas and fecal content A polyp defect is simulated at (A) and a circular spasm resembles a possible early annular carcinoma at (B) The post evacuation film of the same patient eliminates these questions but also shows diverticulosis of the pelvic colon not seen in the completely overdistended barium filled bowel

some other part of the colon but the chance of precipitating an obstruction is much greater than the small chance of demonstrating a second neoplasm in another area of the bowel

3 *Post evacuation film* is an indispensable part of the colon study Occasionally there is considerable barium retention throughout the colon, this is often the case in a very large atonic type of bowel In a spastic and irritable colon, the cleansing effect of the colon is almost complete There is a resulting shortening and contracture of the bowel and there is very generally a widespread coating of the mucosal folds with barium so that a beautiful outline of the mucosal folds can be seen Such a film portraying the mucosal folds is invaluable particularly if there is any question of an intraluminary mass or a possible polypoid process If the elimination is not entirely satisfactory, a

the reduplicating long, floppy, dilated, redundant pelvic colon Compression, manipulation and rotation may not always satisfactorily separate or unfold these reduplications and a small, annular, non-obstructing defect may not be detectable or demonstrable Reexamination after evacuation of the barium enema very often results in a marked shortening and contracture of the colon



Fig 245 Acute overlapping of a jagged saw toothed bowel as a result of an extensive diverticulosis The overlapping margins (A) present an outline of a malignant defect but the angle of rotation (B) eliminates this possibility as does also the post evacuation film (C)

so that the reduplications are very much diminished and a satisfactory delineation of each isolated loop may be obtained It may be necessary to carry out the procedure of filling and emptying two or three times before an unqualified interpretation as to the presence or absence of disease can be clearly stated Such shortening and contracture sometimes occurs even in the very atonic type of colon

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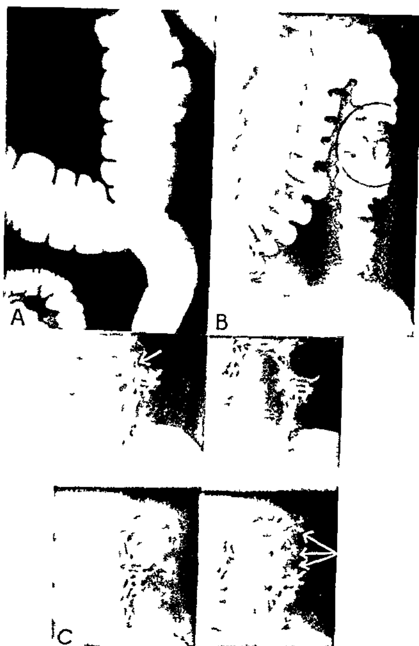


Fig 247 The overlap of the splenic flexure (A) region covered a vigorous but transient spasm thought to be related to an isolated diverticulum at this site (B) this spasm persisted on three consecutive occasions the mucosal pattern in (C) was slightly but persistently distorted Operation showed an early carcinoma

second filling of the bowel will frequently produce the desired results Repeated examinations of this type should be done if there is a question of a polypoid lesion

Diverticulosis and polyposis are frequently seen more clearly and definitely in the post evacuation film than in the routine barium enema study (Figs 245–250)

4 *Contrast air* studies are invaluable and must be done routinely when there is a question of unexplained bleeding Air injection after evacuation of a barium enema is only satisfactory if the colon has been largely cleared of the barium water mixture It is an excellent procedure for demonstrating polypoid defects It should not be done as a routine procedure unless there is some definite indication with respect to a possible very early lesion which cannot be demonstrated by routine barium enema studies It should be emphasized that many artefacts may occur with contrast air These artefacts are in the nature of small barium or fecal masses or air pockets in reduplications These questions must always be eliminated by confirmatory studies



Fig 248 Overlap in (A) fails to show the clear-cut defect seen in the post evacuation film in (B) in pelvic colon

PREPARATION OF THE PATIENT

An x ray study of the colon is generally more satisfactory after a thorough cleansing either by a laxative or enema of water and soapsuds Unfortunately, this preliminary cleansing often results in accentuating the irritable characters at time of fluoroscopy but more often interferes markedly with a satisfactory, homogeneous filling of all parts of the colon because of the resulting excess of gas and fluid retention which so frequently are associated with a partial elimination of a laxative or enema Castor oil gives very satisfactory results When a dye study of the gallbladder supplements a gastrointestinal study there is usually a very satisfactory cleansing effect of the gallbladder dye

Preliminary cleansing of the colon may delay an x ray examination and this is an important factor for the hospital patient

As a rule, no previous preparation is desirable for the ambulatory or office patient The opaque enema or barium water enema may be used for cleansing as well as for diagnosis If the colon is found to be filled with gas and

fecal content, and if the opaque enema procedure fluoroscopically is not entirely satisfactory, it can be immediately repeated after evacuation

The 'plain" or "scout film of the abdomen is an accurate record of an obstructing process An enormous and widespread distribution of gas may cause confusion as to the question of large or small bowel obstruction The



Fig 249 Overdistended colon is negative except for a vague transient spasm in the right transverse colon (A) the post evacuation film shows three polyps in the right middle and left regions of the transverse colon (B) these polypoid defects are accentuated by contrast air studies (C) the larger one in the mid region is movable over a wide range due to a long pedicle attachment

outline of the valvulae conniventes and the resulting 'herringbone' pattern are typical effects of gas in the small intestines This may be marked and the overlapping of the small and large bowel gas makes the differentiation uncertain and sometimes impossible This appearance is very generally a controversial issue and since it is almost a daily occurrence in the average large hospital, the problem can be quickly settled by an opaque enema study

There is hardly any patient who is so ill as to contraindicate such a procedure and it helps to identify the approximate region of obstruction very quickly Since these patients are usually emergency problems, the enema study can be carried out before the patient is assigned to a bed in preparation for operative intervention



Fig 250 Three different patients A B C illustrating the advantage of demonstrating polyps in the post evacuation films without contrast air This examination must generally be repeated several times for evidence and for confirmation

The question of volvulus and intussusception usually presents a fairly typical deformity and requires very little additional work if the technical results are satisfactory

SUMMARY

1 A doubtful or persistent indeterminate defect requires usually a repeat study and the question of operative intervention should be considered in conjunction with the clinical and physical findings particularly if indeterminate questionable findings are persistent

2 Patience and perseverance are necessary if the high standard of good technical detail and results are to be maintained in routine or special x ray

examinations of the colon It is necessary to follow a rigid, routine procedure and to practice repetition of the examination when there is a question of doubt

3 Carcinoma may complicate a chronic ulcerative colitis or diverticulitis or sigmoiditis and these possibilities must be considered in every routine examination of this kind

PRINCIPLES OF THE SURGICAL MANAGEMENT OF COLONIC CARCINOMA

CALVIN M SMYTH, JR , M D

The principles of surgical management of colonic cancer may be stated briefly These are the removal of the disease with the paths of extension along the blood vessels and lymphatics This is not the time or place to discuss specific operations, or surgical technic, but rather to adhere to the subject as it appears in the program

PREPARATION OF THE PATIENT

One of the first principles in the surgical management of colonic cancer is proper preparation of the patient, and with all humility I say to this group of gastroenterologists and medical men that this is properly the job of the surgeon Some of the unpleasant, not to say disastrous results following operations for colonic cancer are the direct consequence of inadequate preparation, and sometimes this is because the surgeon is not permitted, for one reason or another, to obtain the kind of preparation that he requires The success of any operation for carcinoma of the colon depends on the successful execution of the operation without the production of postoperative obstruction or infection either in the wound or at the site of the removal of the growth In order to accomplish this we require that the patient be brought to operation with an empty bowel and at least a mechanically clean bowel, and preferably a bowel which has had the bacterial content reduced to the minimum, it s not possible to operate always upon a sterile bowel

The other important thing in the preparation is the nutritional state of the patient, which I am perfectly willing to let you gentlemen take care of, if you will do it, but I do not think that any patient who is going to be subjected to an operation upon the colon should be brought into the hospital one or two days before operation, no matter how adequate the preparation has been on the outside, and then laid down and cut The patient who is being prepared to withstand a major surgical operation of this sort should have been for at least a week, possibly a little longer, on a high caloric diet containing ample protein and carbohydrate and a minimum of residue This type of diet can nearly always be given to patients who have obstruction as a minimum fac-

tor in the disease, it s not always possible where obstruction is a major factor In preparation of the bowel we may resort to mechanical cleansing and to bacteriostatic measures Sometimes we cannot employ both simultaneously, if obstruction is a major factor it may be possible to get the bowel physically empty by repeated irrigations, and small doses of mild aperients That cannot be done at the same time when one is administering either sulfa drugs or antibiotics in order to obtain bacteriologic cleanliness That is what I meant when I said that sometimes disastrous results were the result of inadequate preparation Too often inadequate preparation means that there has been an attempt to save time, and I m sure that everyone who has had such experience will agree that time so saved is saved at the expense of longer hospitalization, discomfort and sometimes disaster

Therefore if we are dealing with a bowel in which there is a moderate amount of obstruction, the patient should be cleaned out mechanically first and then it s all right to go ahead with the administration of sulfa drugs and antibiotics

Our present practice in the preparation of these patients with a moderate amount of obstruction is to give a small dose of saturated solution of sodium phosphate (by a small dose I mean 2 to 4 drams every morning before any other food is taken), and to follow this late in the afternoon with a tap water enema This will result in mechanical cleansing, but if one gives streptomycin or sulfathalidine or something of that sort on which we are depending for the local action, of course it is not going to do any good because it is promptly washed out Therefore these drugs should be started after mechanical cleansing has been accomplished Streptomycin, by mouth in doses of 2 gm (in quarter gram partitions) daily will benefit a bowel which has a minimum of fecal material, what there is will have very little odor and is usually of a thin and pasty quality and does not bother the surgeon at the time of operation

CHOICE OF OPERATION

So much for preparation As to the nature and extent of the surgical procedure here again a great deal depends upon whether or not obstruction is present in a major or minor degree All of the operations, as I said in the beginning, have as their objective the removal of the disease with the adjacent lines of spread This may be accomplished in many different ways

First we have the operations which are purely and simply decompressive in nature This is for the case that has a great deal of obstruction, amounting to almost complete obstruction Here no procedure should be undertaken until the bowel proximal to the growth has been completely decompressed or defunctionalized by means of a colostomy, and the location of that colostomy will depend upon the location of the lesion For anything in the transverse colon one has little or no choice, we must make the decompression the ascending colon Cecostomy is an unsatisfactory and inadequate procedure For anything beyond the distal transverse colon, which includes the splenic flexure, the descending colon or the sigmoid, we prefer a transverse colostomy

Colostomy may be, in some cases, the only operation that can be done, in which case it becomes not a preliminary stage of a staged procedure but a purely palliative procedure which palliates only one symptom, namely obstruction It follows that one cannot expect to get any great satisfaction from such a procedure But as a preliminary to definitive surgery, colostomy is one of the most valuable additions to the surgeon s armamentarium It will often make possible resection and immediate anastomosis for a lesion in the descending colon or sigmoid which could not possibly have been approached that way without the preliminary colostomy For cases where obstruction is not complete and if the lesion is *in the right colon one may employ a short circuit*, such as an ileotransverse colostomy, as the first stage of a staged procedure

The ideal operation, of course, is one in which the patient has been adequately prepared and in which the surgeon has an empty and clean bowel *with which to work, and in such cases it's perfectly possible and feasible to* do a resection with immediate anastomosis This has the advantage of reducing the time of hospitalization, it permits the removal, as a rule, of more bowel than some of the other staged procedures and it permits wider removal of the mesentery and glands adjacent to the lesion This is possible, however, *only in the best risk patients with the best preparation and too often it is not* possible to give the best operation to everyone

For those patients in whom obstruction has been a factor but not a major factor, where the general state of nutrition is not too good and where the preparation has not been as complete, we must resort to some sort of staged procedure *I have mentioned two preliminary stages, namely colostomy or* short-circuiting anastomosis, but the commonest type of operation performed is the so-called obstructive resection, commonly referred to as Mikulicz s operation However, what is referred to today as the Mikulicz procedure resembles only in one feature the classical operation described by that surgeon *The classical Mikulicz operation consisted in nothing more than the* exteriorization of the involved loop of colon and the closure of the wound about that exteriorized loop after resuturing the proximal and distal bowel together within the abdomen The growth was exteriorized but the bowel was not obstructed and the growth was not removed at that operation The *classical Mikulicz procedure disregarded entirely the adjacent mesentery* and was definitely not an adequate operation for cancer

The obstructive resection as performed today, and sometimes spoken of as the Rankin obstructive resection, is a completely adequate cancer operation, but it consists in the wide mobilization of the involved colon and the adjacent mesentery *with the exteriorization of a good deal of bowel*, and by adequate I mean 5 or 6 inches on either side of the growth, the exteriorization of that amount of bowel, the removal of the mesentery attached to that segment, then the approximation of serosa to serosa within the abdomen and closure of the wound When the wound is closed, clamps are applied to the two loops of bowel *and the growth* with the involved mesentery and any glands is removed at the first sitting

It is sometimes necessary to add a complementary cecostomy to this procedure if the patient s bowel has not been emptied out completely I know Dr Bockus does not think much of complementary cecostomy and with that I am in complete accord However as I have said, we cannot always do exactly as we would like to do and cecostomy, while far from an ideal procedure, may still salvage a bad situation If it is not done under some circumstances it has to be done under emergency conditions after the resection which is never a very good thing

In this type of obstructive resection after the bowel has become firmly adherent to the wound, continuity is restored by cutting out the spur by the application of a crushing clamp

Those who advocate resection with immediate anastomosis in practically every case, contend that it saves the patient a great deal of time A patient with a good anastomosis can certainly get up within a few days and is out of the hospital very shortly but he may also be out of the hospital in a highly polished wooden box and out the back door instead of the front, so I think that it is silly for any surgeon to say he always does resection and anastomosis or that he never does it The whole thing depends upon the presence or absence and the degree of obstruction

Our own experience is that we do resection and anastomosis in about 60 per cent of our cases of colonic cancer and the obstructive resection in 40 per cent (those figures are rough and not absolute) In about 10 per cent of cases, regardless of which method of definitive surgery is employed, we find it necessary to employ some sort of preliminary decompression Both the Rankin obstructive resection and resection with immediate anastomosis give good results The mortality, particularly in the indifferent or poor risk is distinctly higher with resection and immediate anastomosis than it is with the obstructive resection and the reason is not far to seek The cause of mortality in most of these patients is peritonitis It is not peritonitis due to contamination at the time of operation, therefore I think it is silly to argue about the merits of the open type of anastomosis as opposed to a closed type of anastomosis That doesn t make any difference—the type of the anastomosis that a surgeon does is the one which in his hands has proved to give him the best results The peritonitis following resection and anastomosis of the colon is due to a continuing slow leak either from an improperly made anastomosis or an anastomosis which does not heal, and there of course, is an illustration of the paramount importance of proper nutritional preparation for these patients You can make a beautiful anastomosis, technically perfect, in a patient who has no healing power and that patient will die of peritonitis just as surely as the sun will rise

In patients in a poor state of nutrition with or without obstruction, we prefer the obstructive resection because that operation has no mortality outside of the mortality of operation per se You cannot give 100 people anesthesia or you cannot bring 100 people up to an operating room and not have somebody die and the only one who claims he can is the surgeon who either is economizing the truth or who does not do any surgery The results, from

the standpoint of future bowel function, are equally good in both types of operation

SUMMARY

In conclusion may I reiterate that the principles of the surgical management of carcinoma of the colon are (1) to have the patient in the best possible state of nutrition before any operation, (2) to operate only upon a bowel which is physically and bacteriologically clean, (3) to remove the growth with a wide margin on either side together with the adjacent mesentery and (4) to restore continuity either by immediate anastomosis or by the creation of a spur and its later destruction after the technic of Mikulicz

Presentation of Cases

CLINICAL, RADIOLOGIC, SURGICAL, PATHOLOGIC CONFERENCE

GRADUATE HOSPITAL STAFF

DR ROBINSON The first patient we wish to consider this morning is a twenty nine year old white man admitted to Graduate Hospital on November 22 with a complaint at that time of fever rectal pain and purulent dis charge from a rectal abscess This man had been perfectly well until three months after his marriage when in November 23 1943, he had an abrupt onset of diarrhea which persisted with increasing amounts of mucus and in about a two week period of time became blood tinged

He was hospitalized about a month after the onset of this diarrhea at another hospital in the city for about a month Sigmoidoscopy and other studies were done, the diagnosis of chronic ulcerative colitis was made at that time and in the patient s words, he was sent home to die

He was readmitted at that hospital four months later where more extensive studies were performed including a barium enema, which confirmed the impression that the whole colon was involved with ulcerative colitis He was discharged unimproved having about fifteen to twenty stools a day with mucus and occasionally blood noted in the stool He was having intermittent episodes of fever and anorexia, but he had no abdominal pain A month later in June of 1944 he was admitted to another hospital in the vicinity of this city, for a thirteen-week period in which he was managed with bland diet, penicillin and one of the sulfonamide preparations

At the time of discharge from this hospital he was having about six stools a day Shortly after his discharge he had recurrence of more severe diarrhea which persisted intermittently until his readmission to the same hospital in November of 1944 at which time a double barrelled ileostomy was done He had a rectal abscess at that time, and after his discharge from the hospital he persisted with discharge of a milky purulent material from the rectum as well as occasional appearance of blood

This condition persisted although he was able to gain weight He evidently had a well functioning ileostomy for which he wore a bag that fitted flush on the skin, the Rutzen type bag was not possible to use because of the double barrelled ileostomy

He was finally readmitted to this same hospital in December 1947 three years after his first admission, for fever, perianal and rectal pain which radiated to the buttock and upper legs He was experiencing pain on walking

or sitting, ultimately a perirectal abscess drained spontaneously and he was discharged

At this time he was given penicillin, of which he was taking 300,000 units a day until two weeks before his admission here on the 22nd of November At this time he again experienced severe rectal pain, tenderness and fever The pain radiated to the buttocks and upper thighs

Two days before admission he had an acute febrile episode with anorexia and vomiting, and he was admitted because of a large perirectal abscess with an old fistula that had once before been opened and a fresh ischiorectal abscess

Physical findings at the time of admission revealed a well nourished man who was acutely febrile and toxic, showing some laceration of the skin around the area of the ileostomy and the large perianal collection

DR BOCKUS Dr Ferguson, will you describe the emergency operative procedure performed for the ischiorectal abscess?

DR FERGUSON When this man was examined, it was impossible to do anything more than look at him He wouldn't let you touch him The abscess was as Dr Robinson described, it included the tract of the entire right side of the perianal area Under anesthesia, this abscess was explored and incision and drainage were performed The abscess extended upward along the anterior perineum almost to the base of the scrotum and posteriorly almost to the coccyx The abscess cavity was large enough to permit the introduction of a fist The entire ischiorectal fossa formed the cavity of the abscess on the right side of the anal canal

At the time of anesthesia we attempted to enter the anal canal and were able to introduce a finger there for a short distance but we were not able to introduce the finger full length The abscess was simply packed and drainage introduced

Following his operation, the fever subsided somewhat, but he continued to have a hectic temperature We were able, however, to give him hot sitz baths and hot local applications, so that his discomfort gradually decreased over a period of a week He stopped vomiting, was able to eat, and the ileostomy functioned normally

Then we decided to study him An attempt was made to introduce a small catheter into the anal canal in order to fill the colon with barium This was unsuccessful in that the catheter met an obstruction and no barium could be introduced Therefore, a small catheter was introduced through the distal end of the "double-barrel ileostomy into the cecum, and by this method the colon was visualized

DR. FINKELSTEIN One can see the very advanced involvement throughout the colon consisting of marked shortening, marked degree of narrowing, marginal irregularities and, where visualized, a great deal of mucosal distortion (Fig 251) In addition, there were three extracolonic collections of barium, one overlying the midsacral area, a second projecting from the proximal descending colon and a third projecting upward from the mid transverse colon, representing barium in fistulous tracts The most marked extracolonic

collection of barium was that in the midsacral area as a result of a fistulous tract leading from the sigmoid

Dr Bockus I should like to make several comments One must be cautious in the interpretation of barium enema films following ileostomy in terms of fibrosis to account for marked narrowing, because after the colon has been put at rest by ileostomy it is not unusual to find extreme narrowing which suggests advanced fibrosis but which may be due to the atrophy of disuse It is not possible to make a diagnosis of fibrosis of the colon on a patient who

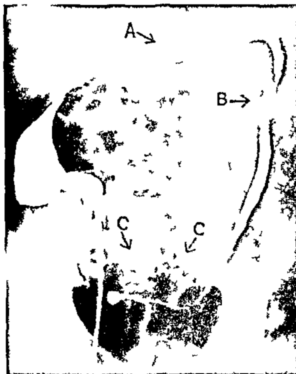


Fig 251 Barium enema obtained by injection of barium via ileostomy Note extreme narrowing and shortening and presence of three fistulous tracts—transverse colon (A) upper descending colon (B) and sigmoid (C)

has had an ileostomy for six months or longer merely on the basis of shortening narrowing or smoothness of the colonic outline You have to have a good mucosal study as well, in order to appraise the pathologic status of the colon

In this instance there is no doubt concerning the extensiveness of the disease in view of the fact that he shows one of the unfortunate complications of chronic ulcerative colitis perforations with pericolonic collections and fistulization Once that stage is reached there is no doubt in the mind of even the most conservative internist that colectomy at the ideal time is required

This young man unfortunately has the disposition which is quite typical of some patients with ulcerative colitis, a very worrisome patient, a boy who has been frightened repeatedly by the prospect of further surgery and who has been in a chronic state of fright throughout his stay

I should also like to discuss one other phase of this problem, namely when is the ideal time for further surgery? I have seen quite a number of patients who have had perirectal abscesses drained as the result of ulcerative colitis I had hoped that in this patient after the drainage of the abscess he would become afebrile and we could then get him into the best possible condition nutritionally and mentally before going ahead with radical resection That was more or less what I had in mind with this patient Unfortunately, he did not continue to improve after the first week, and one wondered whether this was entirely due to the lack of complete drainage of this large abscess Dr Ferguson has stressed the point that this was a very extensive abscess, that it was in communication with the lower end of the colon and he did not anticipate that the opening of the abscess and draining it was going to make it possible for the patient to become afebrile, which I should have preferred before considering the more radical colectomy When we met each other in the corridor the other day, he convinced me that because of the degree of internal fistulization and sepsis he doubted very much if we could get the patient into any better condition than he was in at this time, so that he was operated upon this morning, which I presume is about two weeks following the opening of his abscess Now, Dr Ferguson, will you tell us what you did

DR FERGUSON At operation this morning we attempted to preserve his 'double-barrel ileostomy which was functioning well To do this we had to divide the distal loop of the ileum, the ileum that goes from the ileostomy down to the cecum in a double barrel operation, and turn in that distal ileum This is only possible if there is enough distal ileum to turn in, but his 'double-barrel ileostomy was made about 2 inches from his ileocecal valve, so that there was no terminal ileum that could be turned in Consequently first of all we had to revise his ileostomy, which we did by taking it down, then we were able to free up his colon to the mid transverse colon without much difficulty At the mid-transverse colon a hard mass was encountered, to which omentum and gastrocolic omentum were fixed It took a little time to divide this, and I wasn t at all sure at the time of operation whether or not we were dealing with neoplastic degeneration at this point, although in many of these cases, as you know, the mass represents an inflammatory thickening rather than a carcinoma The mass was finally freed and then in dissecting over toward the splenic flexure and downward along the descending colon we entered an abscess at the site of the fistulous tract in the descending colon This abscess did not contain a great deal of pus, but it was surrounded by a mass of indurated tissue and I'm not at all sure this is not carcinoma, but I don t think it is We decided at that point that we had progressed far enough, and so through a stab wound in the loin, a drain was inserted into the abscess cavity, and the descending colon was brought out through the incision, the ileostomy was reformed and the abdomen closed

DR VALDES-DAPENA Here is the specimen At one end is the small portion of ileum, together with the double barrelled anastomosis The cecum is immediately adjacent From the cecum distally the wall of the colon is definitely thickened but soft, soggy and edematous The mucosa itself looks edematous and smoothed out and shows a number of small reddened areas that probably represent focal necrosis In other words the latter are early stages of ulceration Farther on and down to the point where the transection was made the thickening of the wall is very striking particularly at the site of the previous perforation where considerable pericolonic inflammatory tissue is present There is a good deal of scarring and fibrosis and an organic stenosis of the bowel throughout the terminal 12 or 15 cm of the specimen I doubt if there is any carcinomatous change

DR BOCKUS Would you care to comment on the surgical aspects of this problem Dr Hawthorne?

DR HAWTHORNE I agree with Dr Ferguson that surgery was imperative in this case Also that the situation would not subside with the mere drainage of a deep abscess The fistulas and deep abscesses would continue to be active until the colon is resected This case has gone far beyond the point of response to medical aid

Most surgeons are conservative in their attitude toward idiopathic ulcerative colitis and believe that medical treatment should be employed until it is demonstrated that the lesion will not subside In this case, complete colectomy is the only procedure that can be employed In none of our cases have we found it possible to reestablish continuity with the distal sigmoid

I should like to emphasize that I feel very conservative in the employment of surgery in ulcerative colitis We do save lives with colectomy and the general physical condition does improve in most instances However, we have experienced postoperative complications in about 25 per cent of the cases An ileostomy is not a very pleasant thing for the patient to endure and I think that we should allow the gastroenterologist to employ every means at his command before we consider a colectomy and an ileostomy

DR BOCKUS I presume Dr Ferguson that this case represents another example of progression of the disease following ileostomy? You agree then that the operative findings would justify the conclusion that the walled-off perforations and fistulas appeared some time after the performance of ileostomy Gentlemen this case is another illustration of the failure of ileostomy to halt the progression of the disease and to prevent complications Ileostomy must be followed by colectomy

Dr Smyth would you like to make some comments about this type of problem?

DR SMYTH I know nothing about the case under consideration except what I ve heard this morning but regarding conservatism and radicalism in the management of acute ulcerative colitis I think that the surgeon sometimes has to be radical in order to be conservative I used to talk like all of my other surgical contemporaries about the delay of getting the patient with chronic ulcerative colitis to the surgeon Now we have learned better about

that, because we have found that when we got them early we didn t do much better than when we got them late In other words, anybody with real ulcerative colitis is up against a killing disease and it kills lots of people However, I do believe that surgery should be postponed as long as medical management has anything to offer, bearing in mind that sometimes people die in a great hurry with an acute exacerbation of this condition However, once ileostomy is undertaken, I ve come personally to regard ileostomy as simply the first stage of a colectomy and I ve had some distressing experiences with patients who apparently were doing very, very well after an ileostomy for a considerable time—I mean a year or two years—and then out of a clear sky got a terrific bout of colitis, occasionally we see these people die I do believe that once a patient has had an ileostomy established he should be given a reasonable amount of time to be brought into the optimum condition for the more major procedure, let him get accustomed to his ileostomy and then have his colon removed It s my experience, and I m sure it s the experience of Dr Hawthorne and Dr Ferguson, that the ileostomy itself becomes a much more manageable and supportable condition when the colon has been removed

I think that we can compromise a little regarding the rectum, that is some of these patients get around all right if everything is removed but the rectum Psychologically we can hold out something to these people i e, it still may be possible to anastomose the ileum to the rectosigmoid However, this has more psychologic than practical value, as it is rarely possible

Dr Bockus Incidentally, that is an important point for discussion because it s the thing that we've all done with these patients We tell many of these patients that the rectum and lower sigmoid will be left with the hope but not the promise that perhaps some day the ileum can be joined to the low sigmoid But how many of us have actually had the experience of finding it possible to subsequently go in and reestablish continuity of the bowel and get away with it? Here we have three surgeons In how many cases have you three men been able to reestablish continuity of the bowel when the original disease involved the rectum and sigmoid? Have you, Dr Ferguson, have you, Dr Smyth, have you, Dr Hawthorne? Evidently our surgeons here have had little success with this procedure I suspect that the reports in the literature describing success with reestablishment of continuity of the bowel have been in cases in which the most advanced disease was not in the rectum and sigmoid

Dr Ferguson I should like to say that we, as surgeons, do not see patients in whom this is possible because we do not operate usually until the bowel is so fibrotic that recession of the disease process is never possible

Dr Smyth raised the question as to whether or not early operation was of value We do not know because we never see them early enough really to consider them early I believe that in some clinics early operation has been attempted and in a few cases by early ileostomy, by early diversion of the fecal stream, the inflammatory process in the colon has been demonstrated to have subsided Under such circumstances, I think it is conceivable that either

the ileostomy may be closed or an area of local disease may be excised and a reanastomosis done However, the patients we see are all in such advanced stages that we doubt the feasibility of attempting to reunite them I have one patient whose rectum may recover enough so that we can attempt reanastomosis I should like to reemphasize one other point, namely that ileostomy does not by any means make the rest of the colon well nor does it obviate subsequent complication As Dr Bockus pointed out, the colon tends to con tract when it s not being used and this contraction may be sufficient to produce obstruction I believe that is what happened in this patient It is likely that he has had practically a complete obstruction in his transverse colon, with another obstructing area in the descending colon or perhaps another in the sigmoid Such areas of obstruction in the colon produce a closed loop and I think that is what caused these fistulas and secondary abscesses This is another reason why further radical resection is practically always necessary in patients with ulcerative colitis who have had an ileostomy

DR BOCKUS Perhaps one should mention also that the rectum and low sigmoid must also be removed as a last stage in some patients before they become entirely well Even this short segment of non functioning colon may give rise to sepsis, perforation, bleeding or carcinoma in rare instances

DR THOMAS A JOHNSON I think there is one point that probably ought to be stressed namely, our reluctance to inform patients with ulcerative colitis in whom ileostomy has been performed, of the impracticality of a later anastomosis between the ileum and distal colon I have such a case in which the hope was expressed that sometime in the future she is going to have a hook up job done Now as far as I m personally concerned, she ll never get a hook up job with my consent and yet each time I see her she badgers me with that idea, which was firmly implanted in her mind some time in the past I think that there are enough psychologic problems with these patients without introducing a false concept The patient should be informed that the chances are extremely unlikely that a hook-up will be accomplished

DR. BOCKUS (*Question*) What about the so called double barrel ileostomy?

DR FERGUSON I don t believe a double barrel ileostomy is indicated except in such extremely ill, toxic patients that anything more than the simple incision under local anesthesia and pulling a loop up and doing an ileostomy is indicated Under ordinary circumstances a loop ileostomy is not indicated and it makes subsequent operation much more difficult Witness this situation today This patient was supposed to have had a double barrel ileostomy because he was in such bad shape yet the history is that his appendix was removed at the same operation

One other comment This patient was told by his previous doctor that the mortality from colectomy following an ileostomy was approximately 25 per cent and so you can understand that he was somewhat reluctant to subject himself to further operation I think the best selling point for these patients is to see another patient who has had his colon removed It so happened that we had another patient in the hospital convalescing from colectomy, who

went up to talk to this patient He was in excellent condition and in good spirits Following this visit our patient was anxious to have his operation

DR MONAGHAN I should like to have the surgeon s comment on another phase of the problem One should not get the impression that ileostomy and removal of the colon always end these people s troubles Recently there have been 2 patients that I have followed with ileostomy and total colectomy One of them has had his third intestinal obstruction, the other one is now dead as the result of his second intestinal obstruction

In questioning many of my colleagues, I do not believe that the incidence of intestinal obstruction following ileostomy and ultimate colectomy is exactly to be disregarded I think the occurrence of postoperative obstruction is not insignificant, and has to be taken into account when we are considering operative procedures for ulcerative colitis The other thing that I think you already know, but perhaps it deserves some emphasis, is that in many so-called 'early cases" the disease may be far advanced as revealed by x ray and sigmoidoscopic changes We frequently encounter marked changes in these colons in patients who actually have had symptoms for only six to eight weeks, changes that you would think would require years for their development

DR BOCKUS Do the surgeons deny that intestinal obstruction never occurs after ileostomy? Will you discuss this phase of the problem?

DR FERGUSON No, we do not deny it, we recognize it and we try to avoid it As a matter of fact an amazing thing about these cases is that although you reoperate in the abdomen several times, the incidence of obstruction is not high, and the number of adhesions is remarkably few The intestinal obstruction that I have seen occur following these operations is not usually due to adhesions In performing a colectomy after an ileostomy, a space is left lateral to the ileostomy where the cecum previously was Loops of small gut may enter this space and produce an obstruction Now, knowing that, we take precautions to avoid it When we do a colectomy we obliterate the lateral peritoneal gutter so that the gut can't slip in there If you take that precaution you don t have intestinal obstruction quite so often

DR BOCKUS I believe we have time for the presentation of a second case Dr Robinson, will you give us the pertinent data?

DR ROBINSON This is a story of a thirty-five year old white man who was perfectly well until ten years before he was first seen last March At this time he developed a watery diarrhea consisting of twelve to fifteen bowel movements a day, which began sometime shortly after his marriage After a year his doctor prescribed kaomagma and he was taking a tablespoon of this three times a day It was felt that this was a functional diarrhea because it occurred only on work days (Sundays and holidays were exceptions), so very little attention was paid to this until September 1946, at which time after a brief period in which mucus appeared in the stools, he saw a physician in Baltimore, and was hospitalized for six weeks He was given a three week period of complete stomach rest He was allowed to take nothing by mouth, given 3 liters of amigen and 1 liter of glucose solution parenterally each day

During this period of time he had a remarkable remission in his symptoms, having one to two stools a day which bowel habit persisted for about five months He was put on sulfathalidine therapy which he continued for fifteen months This began in October 1946 and continued until December 1947 The surgical consultant who saw him at this time felt that the involvement of his ileum was too extensive to consider operation

In April 1947 he had the first occurrence of blood grossly in his stools In May of 1947 he had recurrence of pain, this pain was periumbilical In February of this year he had an increase in the frequency of his stools They were occurring six to seven times a day, were watery and for the first time



Fig 252 Film two and three quarter hours after barium by mouth shows dilated ileal loop (A) proximal to diseased terminal ileal segment (B)

he began experiencing bowel movements during the night Pain became worse and for a two week period prior to the first time he was seen here, he noted an increased incidence of nausea and occasional episodes of vomiting The thought was that he was presenting some of the clinical manifestations of an early small bowel obstruction It was at this time that he was first admitted to the Graduate Hospital On physical examination he presented prominent explosive bowel sounds and several palpable distended loops of small bowel Sigmoidoscopy revealed no evidence of ulcerative colitis A progress meal study in March 1948 indicated extensive involvement of the ileum with regional ileitis

DR FINKELSTEIN Barium enema study suggests some coarsening and slight puffiness of the mucosal pattern which causes one to consider the possibility of an early ulcerative colitis of the sigmoid

A few representative films of the small bowel (Figs 252 and 253) during the progress meal study indicate a rather extensive regional ileitis, involving the distal ileum Proximal to this area one notes dilated segments because of partial obstruction Note the peculiar linear shadow due to a communication by fistulous tract between the ileum and sigmoid If we had all of the exposures I think you would recognize that the barium given by mouth gets into the sigmoid before it has had time to go around through the entire colon, so that



Fig 253 Compression film three and a half hours showing diseased loop (A) communicating with sigmoid (B)

the progress meal shows an extensive distal regional ileitis with a fistulous communication into the sigmoid

DR ROBINSON At about the tenth day of his hospitalization, following these studies that have been shown, he began complaining of increasing abdominal pain After two days of this complaint of pain he developed sudden left hemiplegia and left hemianesthesia which were attended with collapse and shock He was followed by the Neurological Service and subsequently showed localizing signs with the persistence of the hemiplegia with the demonstration of a pineal shift, right temporal headache, a percussion note change over the area of his headache and early evidence of papilledema

It was, therefore, thought that he should be explored and a right frontal

trephine was made, twelve days after the onset of this complication A right subtemporal decompression was done Cerebral softening was found with discoloration of the cortex but it was not possible to make a definite diagnosis, and there had been considerable feuding between the neurosurgeons and the neurologists as to whether this represented an early abscess or whether this was an embolic encephalitis

He was subsequently discharged and it was remarkable to note that he was free of abdominal pain he was having one bowel movement a day and there had been a remarkable improvement in his abdominal signs and symp-



Fig 254 Nov 4 1948 Small bowel enema shows diseased terminal ileal loop (A) in communication with sigmoid (B)

toms following this hemiplegic experience He was being followed up with physiotherapy at his home but there was minimal improvement noted in the movement of his left arm and almost no improvement noted in his left leg He had no residual cranial involvement and during the interval from the time of his discharge in April of this year until his readmission the last day of October, he persisted in being symptom free from the intestinal standpoint and experiencing only one formed stool a day

Two weeks before his readmission on the 30th of October of this year he had an isolated experience of abdominal distention which was relieved with

an enema Nothing more was thought of this, it was recalled by the patient a day or so after his admission He had forgotten about this when he came in Thirty-six hours before his admission he developed sharp, sudden umbilical pain, peristaltic and cramping in nature Four hours following the onset of this pain, which persisted, he developed nausea, subsequently vomiting, and during an eighteen hour period until the time he was admitted he was having paroxysmal abdominal pain sharply localized to the umbilicus and almost hourly experiences of nausea and vomiting He was passing no gas but he had a watery bowel movement eighteen hours before admission

In the review of symptoms, there was little to note He had been gaining weight, had a good appetite and, as indicated, one formed stool a day

The physical findings were limited to the abdomen which was distended, there was diffuse umbilical tenderness with a demonstration of rebound



Fig 255 Outside view of resected loop of ileum

tenderness, peristalsis was episodic with rushes occurring synchronously with his peristaltic type of pain The residuals of the hemiplegia were noted The blood count was unremarkable, the first sedimentation rate recorded was 197 mm, this was repeated and was reported in the neighborhood of 90 mm, blood urea at the time of admission was 24, which subsequently was reported normal The rest of his chemical determinations were within normal limits

A Miller Abbott tube was passed the following day under fluoroscopic guidance, he was managed on parenteral fluids, decompressed readily and another view of the small bowel was obtained through the Miller Abbott tube

It is noteworthy that in this exposure made immediately after the completion of the injection of barium (Fig 254) the barium is in the cecum and the proximal ascending colon as well as in the sigmoid colonic area but none in the intervening colon, therefore proving that there is a fistulous com-

munication between the pelvic loop of ileum and the sigmoid The extent of the small intestinal disease is approximately 1½ feet How far proximally the disease extends is a little difficult to estimate because of the dilatation secondary to the obstruction

DR BOCKUS The dilated segment looks very normal to you, doesn t it?

DR FINKELSTEIN The more proximal portion does

DR BOCKUS The diagnosis of ileitis is obvious but I was impressed by the relative shortness of the small intestine It was realized that the length of small intestine often looks short with a Miller Abbot tube threaded through it but I felt rather sure that the normal segment of small intestine was shorter than it should be I couldn t see the usual coil of ileal loops on this series of films or on the previous series and I suspected that there had been another fistula which had actually short circuited about 3 or 4 feet of ileum As a



Fig 256 View of mucosa of entire loop

matter of fact when I talked to Dr Ferguson about it I told him I suspected another fistula higher up short circuiting some of the ileum There wasn t any question about the terminal regional ileitis and the fact that fistulization had occurred into the sigmoid The patient was gotten into condition for operation and referred to the surgeon

DR FERGUSON As is the case with so many of these patients with regional ileitis, the involved intestine is sticky and glues against whatever it contacts This may be bladder or it may be other loops of intestine In this instance it was the terminal ileum which had fallen down into the pelvis and had become glued to the adjacent sigmoid and rectum The whole loop was so fixed in the right side of the pelvis that at first it was a little difficult to determine where the line of cleavage was Eventually we were able to free and deliver it and to determine that the fistula was at the promontory of the sacrum

Gradually the fistula was separated so that the sigmoid and terminal ileum could be easily identified We thought at first that there was only the one fistula, but as a matter of fact there were two fistulas between the ileum and the large gut As a rule when the process extends to another loop of intestine by contiguity, the main portion of the process is in the primarily involved gut and the secondary involvement usually clears up without further surgery Therefore, all we did was to close these fistulas in the sigmoid, oversewing them with peritoneum, and then resect the terminal ileum The disease involved a mass of intestine that was at least 2 feet long or maybe more We attempt when possible to resect the small intestine above the area in which large lymph nodes are found As you all know, ileitis produces tremendous lymph node enlargement which extends down to the root of the mesentery



Fig 257 Close up of muco a showing sharp transition from simply edematous to severely inflamed mucosa

If possible we attempt to resect through normal bowel and above the area of the lymph node involvement This is not always possible but in this instance it could be accomplished

The question as to whether or not the distal involved loop should be dropped and closed and a transverse ileocolostomy performed or whether resection should be performed is one that is still open to debate Usually our position has been that the patients should get along better with their diseased intestine removed, and so in most of our cases we have done primary resection of the involved intestine with primary anastomosis In this patient, where it was not necessary to resect a large amount of ascending colon, we made an anastomosis between the terminal ileum and the ascending colon, an end to-end type This makes a single suture line In a group of some 10 or 11 cases in the last two years we have been able to resect and anastomose in this fashion without a single death I must say that complications are not always

to be avoided in these cases The complications comprise progression of the disease, recurrence of the disease or progression of the disease at the site of the anastomosis, in one of these patients we had to revise and resect again before the patient was through

DR BOCKUS Dr Dapena, do you have the specimen?

DR VALDES DAPENA This is a view of the specimen from the outside (Fig 255) At the proximal portion of the specimen there is smooth and well

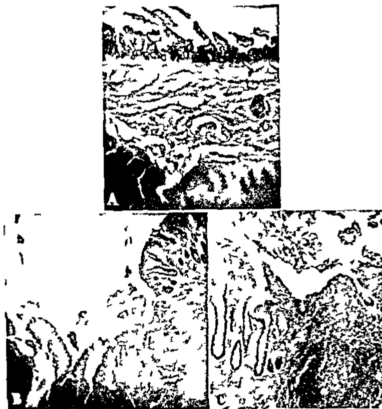


FIG 258 A Section through region just above the line of demarcation of the lesion showing marked submucous edema no inflammatory reaction

B Section through ulcerated mucosa there is severe diffuse round cell infiltration edema persists superficial necrosis causes ulceration

C At area of maximum stenosis the inflammatory infiltration consists of massed lymphocytes in the submucosa and mucosa there is fibrosis in deeper layers

preserved serosa More distally a definite change in appearance is found with the classical invasion of the surface of the bowel by mesenteric fat tissue

Figure 256 shows a view of the open specimen The relatively normal area (*A*) shows thickened folds At one point a sudden change is seen, the mucosa becoming lumpy (*B*) and the wall thicker until it measures 1 cm in thickness at the distal end (*C*)

Figure 257 is a close up of the line of transition The relatively normal side

Gradually the fistula was separated so that the sigmoid and terminal ileum could be easily identified We thought at first that there was only the one fistula, but as a matter of fact there were two fistulas between the ileum and the large gut As a rule when the process extends to another loop of intestine by contiguity, the main portion of the process is in the primarily involved gut and the secondary involvement usually clears up without further surgery Therefore, all we did was to close these fistulas in the sigmoid, oversewing them with peritoneum, and then resect the terminal ileum The disease involved a mass of intestine that was at least 2 feet long or maybe more We attempt when possible to resect the small intestine above the area in which large lymph nodes are found As you all know, ileitis produces tremendous lymph node enlargement which extends down to the root of the mesentery



Fig 257 Close up of mucosa showing sharp transition from simply edematous to severely inflamed mucosa

If possible we attempt to resect through normal bowel and above the area of the lymph node involvement This is not always possible but in this instance it could be accomplished

The question as to whether or not the distal involved loop should be dropped and closed and a transverse ileocolostomy performed or whether resection should be performed is one that is still open to debate Usually our position has been that the patients should get along better with their diseased intestine removed, and so in most of our cases we have done primary resection of the involved intestine with primary anastomosis In this patient, where it was not necessary to resect a large amount of ascending colon, we made an anastomosis between the terminal ileum and the ascending colon, an end to-end type This makes a single suture line In a group of some 10 or 11 cases in the last two years we have been able to resect and anastomose in this fashion without a single death I must say that complications are not always

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shows only a tiny ulcer On the other side the mucosa presents several shallow ulcers, as well as marked swelling

Microscopic sections (Fig 258) show the thickening near the proximal end to be due to submucous edema More distally there is a great deal of lymphoid infiltration under the mucosa with actual follicle formation, together with a great deal of fibrosis in place of edema The serosa in the less involved more proximal portion shows edema and fatty infiltration, in the distal stenotic portion the serosal changes have subsided

Dr Bockus Any giant cells?

Dr Valdes Dapena No giant cells The lymph nodes, by the way, were not very large, the largest was 8 mm, and they showed the usual large follicles with very prominent centers with a great deal of lymphoid hyperplasia